CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-866

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
Department of Health and Human Services  
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

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<tr>
<th>TRADE NAME (OR PROPOSED TRADE NAME)</th>
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<tr>
<th>ACTIVE INGREDIENT(S)</th>
<th>STRENGTH(S)</th>
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<tr>
<td>bromocriptine mesylate</td>
<td>0.8 mg</td>
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DOSAGE FORM

Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration shall be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-writtten or typewriter versions (only) of this report: if additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**F**DA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section 3 and sections 8 and 9.

1. GENERAL

<table>
<thead>
<tr>
<th>a. United States Patent Number</th>
<th>5,716,957</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Issue Date of Patent</td>
<td>2-10-1998</td>
</tr>
<tr>
<td>c. Expiration Date of Patent</td>
<td>2-10-2015</td>
</tr>
</tbody>
</table>

| d. Name of Patent Owner       | VeroScience LLC and The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College |
| Address (of Patent Owner)     | 1334 Main Road |
| City/State                    | Tiverton/RI |
| ZIP Code                      | 02878 |
| FAX Number (if available)     | (401) 816-0524 |
| Telephone Number              | (401) 816-0523 |
| E-Mail Address (if available) | contact@veroscience.com |

| e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(5) and (d)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.93 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) |
| Address (of agent or representative named in f.e.) | |
| City/State | |
| ZIP Code | |
| FAX Number (if available) | |
| Telephone Number | |
| E-Mail Address (if available) | |

**Not applicable.**

- Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  
  - Yes  
  - No

- If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  
  - Yes  
  - No

**Page 1**

FORM FDA 3542z (7/07)

PSC Graphics (38) 445-1899 EF
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? □ Yes □ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? □ Yes □ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). □ Yes □ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) □ Yes □ No

2.6 Does the patent claim only an intermediate? □ Yes □ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) □ Yes □ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? □ Yes □ No

3.2 Does the patent claim only an intermediate? □ Yes □ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) □ Yes □ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? □ Yes □ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? □ Yes □ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Improvement of glycemic control. Claims 1, 2, 4-6 and 8. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. □ Yes
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
04/04/2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder
☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner
☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
S. Peter Ludwig

Address
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City/State
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ZIP Code
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Telephone Number
(212) 527-7770

FAX Number (if available)
(212) 527-7701

E-Mail Address (if available)
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The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. **GENERAL**

   a. United States Patent Number
      - 5,679,683

   b. Issue Date of Patent
      - 10-21-1997

   c. Expiration Date of Patent
      - 10-21-2014

   d. Name of Patent Owner
      - VeroScience LLC and Geneva Pharmaceuticals, Inc.

   e. Address (of Patent Owner)
      - VeroScience LLC

   f. City/State
      - Tiverton, RI

   g. ZIP Code
      - 02878

   h. Telephone Number
      - (401) 816-0525

   i. E-Mail Address (if available)
      - contact@veroscientific.com

   j. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (b)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.98 (If patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

   k. Not applicable.

   Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?
   - Yes [ ]
   - No [X]

   g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?
   - Yes [ ]
   - No [X]
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

### 2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  
☐ Yes  ☐ No

2.2 Does the patent claim a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  
☐ Yes  ☐ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  
☐ Yes  ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.  
Not applicable.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement?  
(Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  
☐ Yes  ☐ No

2.6 Does the patent claim only an intermediate?  
☐ Yes  ☐ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  
☐ Yes  ☐ No

### 3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  
☑ Yes  ☐ No

3.2 Does the patent claim only an intermediate?  
☐ Yes  ☐ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  
☐ Yes  ☐ No

### 4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  
☐ Yes  ☐ No

4.2 Patent Claim Number(s) (as listed in the patent)  

<table>
<thead>
<tr>
<th>Patent Claim Number(s)</th>
<th>Does (Do) the patent claim(s) referenced in 4.3 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?</th>
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<tbody>
<tr>
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<td>☐ Yes ☐ No</td>
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.  

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

### 5. No Relevant Patents

or this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.83. I attest that I am familiar with 21 CFR 314.83 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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[ ] NDA Applicant/Holder

[ ] NDA Applicant/Holder's Attorney, Agent (Representative) or other Authorized Official

[ ] Patent Owner

[ ] Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
S. Peter Ludwig

Address
Darby & Darby, P.C.
7 World Trade Center, 250 Greenwich Street

City/State
New York, NY

ZIP Code
10007

Telephone Number
(212) 527-7770

E-Mail Address (if available)
pludwig@darbylaw.com

FAX Number (if available)
(212) 527-7701

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Rockville, MD 20857

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**Form FDA 3542a (7/07)**

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**1. GENERAL.**

| a. United States Patent Number | 5,468,755 |
| b. Issue Date of Patent | 11-21-1995 |
| c. Expiration Date of Patent | 11-21-2012 |
| d. Name of Patent Owner | The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College |
| Address of Patent Owner | Louisiana State University, Office of Intellectual Property, 203 Boyd Hall |
| City/State | Baton Rouge/LA |
| ZIP Code | 70803 |
| FAX Number (if available) | (225) 615-8965 |
| Telephone Number | (225) 615-8967 |
| E-Mail Address (if available) | oip@lsu.edu |
| e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(5) and (B)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) | |
| Address of agent or representative named in item | |
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**SB.** Not applicable.

* Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  ☐ Yes ☑ No

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---

**FORM FDA 3542a (7/07)**

**Department of Health and Human Services**

**Food and Drug Administration**

**NDA NUMBER**

20-866

**NAME OF APPLICANT/NDA HOLDER**

VeroScience LLC
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2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☑ No

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2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☑ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

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2.6 Does the patent claim only an intermediate? ☐ Yes ☑ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patient novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☑ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☐ Yes ☑ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☑ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☑ No

4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☑ Yes ☐ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☑ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

   (1) Improvement of glycemic control. Claims 1, 2, 4, 6, 8-14, 17-29. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3

   (2) Treatment of Type II diabetes. Claims 8, 10, 11-14, 17-29. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formula or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes
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Name
S. Peter Ludwig

Address
Darby & Darby P.C.
7 World Trade Center, 250 Greenwich Street

City/State
New York/NY

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   a. United States Patent Number  
      5,866,584  
   b. Issue Date of Patent  
      2-2-1999  
   c. Expiration Date of Patent  
      11-21-2012  
   d. Name of Patent Owner  
      The Board of Supervisors of Louisiana State University  
       and Agricultural and Mechanical College  
      Address (of Patent Owner)  
      Louisiana State University, Office of Intellectual Property, 203 Boyd Hall  
      City/State  
      Baton Rouge/LA  
      ZIP Code  
      70803  
      FAX Number (if available)  
      (225) 615-8965  
      Telephone Number  
      (225) 615-8967  
      E-Mail Address (if available)  
      oip@lsu.edu  
   e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (I)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.98 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  
      Address (of agent or representative named in I.a.)  
      City/State  
      ZIP Code  
      Telephone Number  
      E-Mail Address (if available)  
   f. Not applicable.  

    1. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  
       □ Yes   □ No  
    g. If the patent referenced above has been submitted previously for listing, is the expiration date a new aspiration data?  
       □ Yes   □ No  

FORM FDA 3542a (7/07)  
Page 1
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3 If the answer to question 2.2 is &quot;Yes,&quot; do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)

2.6 Does the patent claim only an intermediate?

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)

3. Drug Product (Composition/Formulation)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2 Does the patent claim only an intermediate?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)</td>
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<td></td>
</tr>
</tbody>
</table>

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2 Patent Claim Number(s) (as listed in the patent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-23 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)


5. No Relevant Patents

If this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Yes
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

<table>
<thead>
<tr>
<th>Name</th>
<th>S. Peter Ludwig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>Darby &amp; Darby P.C.</td>
</tr>
<tr>
<td></td>
<td>7 World Trade Center, 250 Greenwich Street</td>
</tr>
<tr>
<td>ZIP Code</td>
<td>10007</td>
</tr>
<tr>
<td>FAX Number</td>
<td>(212) 527-7701</td>
</tr>
<tr>
<td>Telephone</td>
<td>(212) 527-7700</td>
</tr>
</tbody>
</table>

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

- [ ] NDA Applicant/Holder
- [x] NDA Applicant/holder's Attorney, Agent (Representative) or other Authorized Official
- [ ] Patent Owner
- [ ] Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HPD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(b)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(B) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: if additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FSA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

### 1. GENERAL

<table>
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<td>11-21-2012</td>
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<th>d. Name of Patent Owner</th>
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<td>The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College</td>
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</table>

<table>
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<th>Address (of Patent Owner)</th>
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<tr>
<td><a href="mailto:olp@lsu.edu">olp@lsu.edu</a></td>
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<tr>
<th>Telephone Number (if available)</th>
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<tr>
<td>(225) 615-8965</td>
</tr>
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</table>

### e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(6) and 505(b)(7) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.98 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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<th>Address (of agent or representative named in T.R.)</th>
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<tr>
<td>□ Yes □ No</td>
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<tbody>
<tr>
<td>□ Yes □ No</td>
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<th>If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?</th>
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<tbody>
<tr>
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</table>

**FORM FDA 3542a (7/07)**
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  
☐ Yes  ☑ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  
☐ Yes  ☑ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  
☐ Yes  ☑ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement?  
(Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  
☐ Yes  ☑ No

2.6 Does the patent claim only an intermediate?  
☐ Yes  ☑ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  
☐ Yes  ☑ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  
☐ Yes  ☑ No

3.2 Does the patent claim only an intermediate?  
☐ Yes  ☑ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  
☐ Yes  ☑ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  
☑ Yes  ☑ No

4.2 Patent Claim Number(s) (as listed in the patent)  
Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  
☑ Yes  ☑ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

<table>
<thead>
<tr>
<th>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Improvement of glycemic control. Claims 1, 3-20. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3</td>
</tr>
<tr>
<td>(2) Treatment of Type II diabetes. Claims 11, 15 and 20. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3</td>
</tr>
</tbody>
</table>

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  
☐ Yes
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
04/04/2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder
☐ NDA Applicant/Holder’s Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner
☐ Patent Owner’s Attorney, Agent (Representative) or Other Authorized Official

Name
S. Peter Ludwig

Address
Darby & Darby PC.
7 World Trade Center, 250 Greenwich Street

City/State
New York/NY

ZIP Code
10007

Telephone Number
(212) 527-7770

E-Mail Address (if available)
pludwig@darbylaw.com

FAX Number (if available)
(212) 527-7791

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HPD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
EXCLUSIVITY SUMMARY

NDA # 20-866  SUPPL #  HFD # 510

Trade Name  Cycloset

Generic Name  bromocriptine mesylate

Applicant Name  VeroScience

Approval Date, If Known  February 2009

PART I  IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  YES ☑  NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

     YES ☑  NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
d) Did the applicant request exclusivity?  

   YES ☐  NO ☒

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   e) Has pediatric exclusivity been granted for this Active Moiety?  

   YES ☐  NO ☒

   If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

   IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?  

   YES ☐  NO ☒

   IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES  
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

   Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

   YES ☒  NO ☐

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
NDA# 77226  Bromocriptine mesylate 5 mg capsules
NDA# 17-962  Bromocriptine mesylate 2.5 mg tablets
NDA# 77646  Bromocriptine mesylate 2.5 mg tablets

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#
NDA#
NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III  THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of
summary for that investigation.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒
If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

165-AD-04-03-US-1

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not re demonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

Investigation #2

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

Investigation #2
If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

165-AD-04-03-US-1

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

<table>
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<tr>
<th>IND # 34,661</th>
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|              |       | Explain:

Investigation #2

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<th>IND #</th>
<th>YES ☐</th>
<th>NO ☐</th>
</tr>
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</table>
|             |       | Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
Investigation #1

YES □ NO □
Explain: □

Investigation #2

YES □ NO □
Explain: □

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES □ NO □

If yes, explain:

Name of person completing form: Jena M. Weber
Title: PM
Date: 2/2/2009

Name of Office/Division Director signing form: Mary Parks, M.D.
Title: Division Director, DMEP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
2/2/2009 02:30:28 PM
PEDiatric Page

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 20-868  Supplement Number: ____  NDA Supplement Type (e.g. SE5): ____

Division Name: DMEP  PDUFA Goal Date: 10/15/08  Stamp Date: 4/13/2008

Proprietary Name: Cycloset

Established/Generic Name: Bromocriptine Mesylate

Dosage Form: Tablets

Applicant/Sponsor: VeroScience

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) None
(2) ____
(3) ____
(4) ____

Pediatric use for each pediatric subgroup must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: As an adjunct to diet & exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Q1: Is this application in response to a PREA PMR?  Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: ____  Supplement #: ____  PMR #: ____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☒ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. Skip to signature block.

* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. Skip to signature block.

☒ No. Please proceed to the next question.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.
Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)
☒ No: Please check all that apply:
   ☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
   ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
   ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
   ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
   ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

☐ Necessary studies would be impossible or highly impractical because:
   ☐ Disease/condition does not exist in children
   ☐ Too few children with disease/condition to study
   ☐ Other (e.g., patients geographically dispersed): ______

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.
Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Not Feasible*</th>
<th>Not Meaningful Therapeutic Benefit*</th>
<th>Ineffective or Unsafe†</th>
<th>Formulation Failed‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>_ wk. _ mo.</td>
<td>_ wk. _ mo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>0 yr. _ mo.</td>
<td>9 yr. _ mo.</td>
<td>☒</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>_ yr. _ mo.</td>
<td>_ yr. _ mo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>_ yr. _ mo.</td>
<td>_ yr. _ mo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>_ yr. _ mo.</td>
<td>_ yr. _ mo.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.
Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.
Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:
☐ Necessary studies would be impossible or highly impracticable because:
☐ Disease/condition does not exist in children
☒ Too few children with disease/condition to study
☐ Other (e.g., patients geographically dispersed): ______

* Not meaningful therapeutic benefit:
☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:
☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

‡ Formulation failed:
☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderrmhs@fda.hhs.gov) OR AT 301-796-6700.
Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

<table>
<thead>
<tr>
<th>Deferrals (for each or all age groups):</th>
<th>Reason for Deferral</th>
<th>Applicant Certification †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Ready for Approval in Adults</td>
<td>Need Additional Adult Safety or Efficacy Data</td>
</tr>
<tr>
<td>☐ Neonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☒ Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☒ All Pediatric Populations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date studies are due (mm/dd/yy): ______

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: ______

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

If there are questions, please contact the CDER FMHS via email (cdernmhs@fda.hhs.gov) or at 301-796-9700.
### Section D: Completed Studies (for some or all pediatric subpopulations)

Pediatric subpopulation(s) in which studies have been completed (check below):

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
<th>PeRC Pediatric Assessment form attached?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>__ wk. __ mo.</td>
<td>__ wk. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
<td>Yes ☐ No ☐</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.
Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

### Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>__ wk. __ mo.</td>
<td>__ wk. __ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
</tr>
<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.
Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

### Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (odermhst@fda.hhs.gov) OR AT 301-796-9700.
Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
<th>Extrapolated from:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adult Studies?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other Pediatric</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Studies?</td>
</tr>
<tr>
<td>neonate</td>
<td>_wk._mo.</td>
<td>_wk._mo.</td>
<td>No</td>
</tr>
<tr>
<td>other</td>
<td>_yr._mo.</td>
<td>_yr._mo.</td>
<td>No</td>
</tr>
<tr>
<td>other</td>
<td>_yr._mo.</td>
<td>_yr._mo.</td>
<td>No</td>
</tr>
<tr>
<td>other</td>
<td>_yr._mo.</td>
<td>_yr._mo.</td>
<td>No</td>
</tr>
<tr>
<td>other</td>
<td>_yr._mo.</td>
<td>_yr._mo.</td>
<td>No</td>
</tr>
<tr>
<td>all pediatric</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
<td>No</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? □ No; □ Yes.

Are the indicated age ranges (above) based on Tanner Stage? □ No; □ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

(See appended electronic signature page)

Regulatory Project Manager

(Revised: 8/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.
Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: ______

Q1: Does this indication have orphan designation?
☐ Yes. PREA does not apply. Skip to signature block.
☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?
☐ Yes: (Complete Section A.)
☐ No: Please check all that apply:
  ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  ☐ Extrapolation In One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)
☐ Necessary studies would be impossible or highly impracticable because:
  ☐ Disease/condition does not exist in children
  ☐ Too few children with disease/condition to study
  ☐ Other (e.g., patients geographically dispersed): ______
  ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
  ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
  ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
  ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (pedersmb@fda.hhs.gov) OR AT 301-796-0700.
**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

**Note:** If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

<table>
<thead>
<tr>
<th>Reason (see below for further detail):</th>
<th>Not feasible£</th>
<th>Not meaningful therapeutic benefit®</th>
<th>Ineffective or unsafe†</th>
<th>Formulation failed▲</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)?  
☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage?  
☐ No; ☐ Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

☐ Not feasible:
  ○ Necessary studies would be impossible or highly impracticable because:
    - Disease/condition does not exist in children
    - Too few children with disease/condition to study
    - Other (e.g., patients geographically dispersed): ___

☐ Not meaningful therapeutic benefit:
  - Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

☐ Ineffective or unsafe:
  - Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
  - Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
  - Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

▲ Formulation failed:
  - Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, ...
Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

<table>
<thead>
<tr>
<th>Deferrals (for each or all age groups):</th>
<th>Reason for Deferral</th>
<th>Applicant Certification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Read for Approval in Adults</td>
<td>Need Additional Adult Safety or Efficacy Data</td>
</tr>
<tr>
<td>Population</td>
<td>minimum</td>
<td>maximum</td>
</tr>
<tr>
<td>☐ Neonate</td>
<td>_ wk. _ mo.</td>
<td>_ wk. _ mo.</td>
</tr>
<tr>
<td>☐ Other</td>
<td>_ yr. _ mo.</td>
<td>_ yr. _ mo.</td>
</tr>
<tr>
<td>☐ Other</td>
<td>_ yr. _ mo.</td>
<td>_ yr. _ mo.</td>
</tr>
<tr>
<td>☐ Other</td>
<td>_ yr. _ mo.</td>
<td>_ yr. _ mo.</td>
</tr>
<tr>
<td>☐ All Pediatric Populations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
</tr>
</tbody>
</table>

Date studies are due (mm/dd/yy): ________

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: ________

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (pmhssub@fda.hhs.gov) OR AT 301-796-0700.
### Section D: Completed Studies (for some or all pediatric subpopulations)

**Pediatric subpopulation(s) in which studies have been completed (check below):**

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
<th>PeRC Pediatric Assessment form attached?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>wk. ___ mo.</td>
<td>wk. ___ mo.</td>
<td>Yes ☐</td>
</tr>
<tr>
<td>Other</td>
<td>yr. ___ mo.</td>
<td>yr. ___ mo.</td>
<td>Yes ☐</td>
</tr>
<tr>
<td>Other</td>
<td>yr. ___ mo.</td>
<td>yr. ___ mo.</td>
<td>Yes ☐</td>
</tr>
<tr>
<td>Other</td>
<td>yr. ___ mo.</td>
<td>yr. ___ mo.</td>
<td>Yes ☐</td>
</tr>
<tr>
<td>Other</td>
<td>yr. ___ mo.</td>
<td>yr. ___ mo.</td>
<td>Yes ☐</td>
</tr>
<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
<td>Yes ☐</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

### Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

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<th>maximum</th>
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<td>wk. ___ mo.</td>
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<td>yr. ___ mo.</td>
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<td>yr. ___ mo.</td>
<td>yr. ___ mo.</td>
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<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
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</table>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

---

*IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER FMHS VIA EMAIL (nimrambh@fda.hhs.gov) OR AT 301-796-0700.*
Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

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<th>maximum</th>
<th>Extrapolated from:</th>
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<td>Adult Studies?</td>
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<td></td>
<td></td>
<td></td>
<td>Studies?</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? □ No; □ Yes.
Are the indicated age ranges (above) based on Tanner Stage? □ No; □ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (pedrambh@fda.hhs.gov) OR AT 301-796-0700.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
5/1/2009 01:42:04 PM
PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA 20-866

Stamp Date: April 15, 2008

PDUFA Goal Date: October 15, 2008

HFD-510

Trade and generic names/dosage form: Cycloset (bromocriptine mesylate) Tablets 0.8 mg

Applicant: VeroScience

Therapeutic Class: 3

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? * Yes.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication: CYCLOSET is indicated as an adjunct to diet and exercise to improve glycemic control (hyperglycemia) in patients with type 2 diabetes mellitus.

Is this an orphan indication? NO

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☐ No: Please check all that apply: X Partial Waiver X Deferred ___Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population

☐ Disease/condition does not exist in children

☐ Too few children with disease to study

☐ There are safety concerns

☐ Other:____________________________________

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.
Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____
Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☒ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:________________________

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☒ Adult studies ready for approval
☐ Formulation needed
☐ Other:________________________

Date studies are due (mm/dd/yy): To be determined after CLN & STT reviews are completed.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

This page was completed by:

(See appended electronic signature page)
Jena M. Weber
Regulatory Project Manager
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

------------------
Jena Weber
11/10/2008 11:44:59 AM
VeroScience LLC certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Anthony H. Cincotta, Ph. D.
President

April 13, 2008
Date
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑  (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

☐  (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐  (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME
Anthony H. Cirillo, PhD

TITLE
President

FIRM/ORGANIZATION
VeroScience LLC

SIGNATURE

DATE
04/13/2008

Paperwork Reduction Act Statement
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857
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<th>Site Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas Wade, Jr., MD</td>
<td>Columbus Clinic</td>
</tr>
<tr>
<td></td>
<td>610 19th Street</td>
</tr>
<tr>
<td></td>
<td>Columbus, GA 31901</td>
</tr>
<tr>
<td>Sherwyn Schwartz, MD</td>
<td>DGD Research, Inc.</td>
</tr>
<tr>
<td></td>
<td>5107 Medical Drive</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Nizar Daboul, MD</td>
<td>Clinical Research Source, Inc.</td>
</tr>
<tr>
<td></td>
<td>5757 Monclova Road</td>
</tr>
<tr>
<td></td>
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<td>Maumee, OH 43537</td>
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<tr>
<td>Pamela Dugano-Daphnis, MD, MPH</td>
<td>347 East Parkwood Drive</td>
</tr>
<tr>
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<td>Lauro Lapuz, MD</td>
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</tr>
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<td>Todd Winter, MD</td>
<td>Medford Medical Clinic, Inc.</td>
</tr>
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<td></td>
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<td>Medford, OR 97504</td>
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<td>Mark Riederman, MD</td>
<td>1800 Hollister Drive</td>
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<td>Tushar Patel, MD</td>
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<td>Bethany Medical Center</td>
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<td>Reichman and Associates</td>
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<td>Joseph Moran, MD</td>
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<td>Robert Schulman, MD</td>
<td>2441 Ridgecrest Drive Southeast</td>
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<td>Louis Chaykin, MD</td>
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<td>Internal Medicine of Greer</td>
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<td>Diabetes Center of the Southwest</td>
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<td>Yezid Mora, MD</td>
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| Gonzalo Uribe-Botero | 2846 Knight Road  
                  | Bensalem, PA  19020                         |
|                      | Mercury Pharma Services, Inc.  
                  | 6065 Hillcroft Avenue  
                  | Suite 100  
                  | Houston, TX  77081 |
| Greg Coodley, MD     | Fanno Creek Clinic, Inc.  
                  | 2400 Southwest Vermont Street  
                  | Portland, OR  97219 |
| Louis Maletz, MD     | San Diego Managed Care Group  
                  | 11777 Bernardo Plaza Court  
                  | Suite 206  
<pre><code>              | San Diego, CA  92128 |
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<tr>
<td>Francis Agnone MD</td>
<td>Internal Medicine Physicians Assoc., PC</td>
</tr>
<tr>
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<td>1515 N. 9th Street Suite A</td>
</tr>
<tr>
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<td>Phoenix AZ 85006</td>
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<tr>
<td>Meera Amar MD</td>
<td>Diabetes &amp; Endocrine Center</td>
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<tr>
<td>Corey Anderson MD</td>
<td>Dedicated Clinical Research</td>
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<td>10474 W. Thunderbird Blvd. Suite 200 &amp; 201</td>
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<tr>
<td>Harold Bays MD</td>
<td>L-MARC Research Center</td>
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<td>Bruce Bowling MD</td>
<td>Regional Clinical Research, Inc.</td>
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<tr>
<td>Paul Bristol MD</td>
<td>Benchmark Research Austin</td>
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<tr>
<td></td>
<td>2013 Wells Branch Parkway Suite 113</td>
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<tr>
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<td>Austin TX 78728</td>
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<tr>
<td>Dennis Buth MD</td>
<td>Professional Research Network of Kansas</td>
</tr>
<tr>
<td></td>
<td>345 Riverview #400</td>
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<td></td>
<td>Wichita KS 67203</td>
</tr>
<tr>
<td>Jambur Chandrashekar MD</td>
<td>81-719 Dr. Carreon Drive Blvd. Suite B1</td>
</tr>
<tr>
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<td>Indio CA 92201</td>
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<tr>
<td>Teresa Costa MD</td>
<td>Benchmark Research Austin</td>
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<td>1015 East 32nd Street Suite 303</td>
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<tr>
<td>Pankaj Desai MD</td>
<td>Crossroads Research, Inc.</td>
</tr>
<tr>
<td></td>
<td>25 Crossroads Drive #410</td>
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<td>Owings Mills MD 21117</td>
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<tr>
<td>Robert Ealy MD</td>
<td>Midwest Institute of Health Awareness</td>
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<tr>
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<td>Hickory NC 28601</td>
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<tr>
<td>Philip Emrie MD</td>
<td>Rocky Mountain Center for Research</td>
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<td>Wheat Ridge CO 80033</td>
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<tr>
<td>John Ervin MD</td>
<td>The Center for Pharmaceutical Research</td>
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<td>1010 Carondelet Drive Suite 220</td>
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<td>Cecil Farrington MD</td>
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<td>401 Mocksville Avenue Suite 300</td>
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<td>Jerome Fischer MD</td>
<td>DGD Research, Inc.</td>
</tr>
<tr>
<td></td>
<td>803 Castroville Road Suite 140</td>
</tr>
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</tr>
<tr>
<td>Steven Folkert MD</td>
<td>Clinical Research Center of Nevada</td>
</tr>
<tr>
<td></td>
<td>1022 East Sahara Ave.</td>
</tr>
<tr>
<td></td>
<td>Las Vegas NV 89104</td>
</tr>
</tbody>
</table>

529
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Site Address</th>
</tr>
</thead>
</table>
| Neil Fraser MD       | Troy Internal Medicine
                      4550 Investment Drive Suite 210
                      Troy MI 48098                                                               |
| Lawrence Gassner MD  | Tatum Ridge Internal Medicine
                      18404 N. Tatum Blvd. Suite 205
                      Phoenix AZ 85032                                                            |
| Carl Griffin MD      | Lynn Health Science Institute
                      5300 N. Independence Suite 130
                      Oklahoma City OK 73112                                                       |
| Charles Herring MD   | New Hanover Medical Research
                      1907 Tradd Court
                      Wilmington NC 28401                                                          |
| Darrell Herrington DO | Benchmark Research San Angelo
                        3555 Knickerbocker Road
                        San Angelo TX 76904                                                          |
| Stephen Hippler MD   | OSF Medical Group
                      8600 North State RTE 91 Suite 130
                      Peoria IL 61615                                                              |
| Harry Larkin MD      | Island Medical Professional Association
                      1812 Long Beach Blvd.
                      Ship Bottom NJ 08008                                                         |
| Kurt Lash MD         | Lynn Institute of the Rockies
                      2500 North Circle Drive Suite 300
                      Colorado Springs CO 80909                                                    |
| James Lieber MD      | 595 N. Dobson Suite D-76
                      Chandler AZ 85224                                                             |
| Timothy Linder MD    | Prime Care Medical Center
                      One Prime Care Drive
                      Selmer TN 38375                                                               |
| Thomas Littlejohn III MD | Piedmont Medical Research
                      1901 S. Hawthorne Road Suite 306
                      Winston-Salem NC 27103                                                        |
| N. Martin Lunde MD   | Twin Cities Clinical Research
                      6200 Shingle Creek Parkway S-300
                      Brooklyn Center MN 55430                                                     |
| Scott Meyers MD      | Heartland Research Associates, LLC
                      1709 South Rock Road
                      Wichita KS 67207                                                              |
| Richard Mills MD     | Palmetto Medical Research
                      900 Bowman Road Suite 201
                      Mt. Pleasant SC 29464                                                         |
| Manuel Modiano MD    | Arizona Clinical Research Center
                      1825 N. Kolb Road
                      Tucson AZ 85715                                                               |
| David Morin MD       | Triticites Medical Research
                      1958 W. State Street
                      Bristol TN 37620                                                              |
| Julio Pagan MD       | MedSouth HealthCare
                      1700 Woodlawn Avenue
                      Dyersberg TN 38024                                                            |
<table>
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| James Payne MD         | Jackson Clinic  
2863 Highway 45 Bypass North  
Jackson TN 38305                                                            |
| Geri Poss MD           | Innovative Clinical Trials  
5430 Fredericksburg Road Suite 400  
San Antonio TX 78229                                                         |
| George Raad MD         | Metrolina Medical Research Associates  
1700 Abbey Place Suite 209  
Charlotte NC 28209                                                            |
| Patrick Rask MD        | New Hope Research of Oregon  
9045 SW Barbur Blvd. Suite 106  
Portland OR 97219                                                              |
| Marc Rendell MD        | Creighton University  
Diabetes Center, #6715  
601 North 30th Street  
Omaha NE 68131                                                                 |
| L. Edward Roberts, Jr. MD | Central Kentucky Research Associates, Inc.  
3475 Richmond Road 3rd Floor  
Lexington KY 40509                                                              |
| Jeffrey Rosen MD       | Clinical Research of South Florida  
275 Alhambra Circle  
Coral Gables FL 33134                                                         |
| Eli Roth MD            | Sterling Research Group  
2230 Auburn Ave. Level B  
Cincinnati OH 45219                                                             |
| John Rubino MD         | Triangle Medical Research Associates  
3509 Haworth Drive Suite 300  
Raleigh NC 27609                                                                 |
| Steven Russell MD      | Graduate Hospital  
1800 Lombard Street Suite 501  
Philadelphia PA 19146                                                         |
| Robert Schreiman MD    | Apex Research Institute  
999 North Tustin Avenue Suite 120  
Santa Ana CA 92705                                                              |
| Sherwyn Schwartz MD    | DGID Research, Inc.  
5107 Medical Drive  
San Antonio TX 78229                                                            |
| William Seger MD       | Benchmark Research Fort Worth  
4450 Boat Club Road Suite 300  
Fort Worth TX 76135                                                             |
| Danny Sagimoto MD      | Cedar Crosse Research and Healthcare  
800 South Wells Suite M15  
Chicago IL 60607                                                                 |
| Allen Sussman MD       | Rainier Clinical Research Center  
723 S.W. 10th Street Suite 100  
Renton WA 98055                                                                  |
| Phillip Toth MD        | Midwest Institute for Clinical Research  
8935 North Meridian Street Suite 230  
Indianapolis IN 46260                                                           |
| Sunil Verma MD         | Sunil P. Verma, M.D., MPH, Inc.  
300 Tollgate Road Suite 207  
Warwick RI 02886                                                                |
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Site Address</th>
</tr>
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<tbody>
<tr>
<td>Aaron Vinik MD</td>
<td>The Strelitz Diabetes Institutes</td>
</tr>
<tr>
<td></td>
<td>Eastern Virginia Medical School</td>
</tr>
<tr>
<td></td>
<td>855 West Brambleton Avenue</td>
</tr>
<tr>
<td></td>
<td>Norfolk VA 23510</td>
</tr>
<tr>
<td>Ralph Wade DO</td>
<td>Advanced Clinical Research-Bountiful</td>
</tr>
<tr>
<td></td>
<td>425 Medical Drive Suite 207</td>
</tr>
<tr>
<td></td>
<td>Bountiful UT 84010</td>
</tr>
<tr>
<td>Robert Anderson MD</td>
<td>Omaha VAMC</td>
</tr>
<tr>
<td></td>
<td>4101 Woolworth Ave</td>
</tr>
<tr>
<td></td>
<td>Research Service 151</td>
</tr>
<tr>
<td></td>
<td>Omaha NE 68105</td>
</tr>
<tr>
<td>Sunil Asnani MD</td>
<td>New Orleans VAMC</td>
</tr>
<tr>
<td></td>
<td>1430 Tulane Ave</td>
</tr>
<tr>
<td></td>
<td>Dept of Endo SL-53</td>
</tr>
<tr>
<td></td>
<td>New Orleans LA 70112</td>
</tr>
<tr>
<td>Elena Barengolsa MD</td>
<td>Chicago Westside VAMC</td>
</tr>
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<td></td>
<td>CHCS Westside</td>
</tr>
<tr>
<td></td>
<td>820 S. Damien Ave M/C111 Chicago IL 60652</td>
</tr>
<tr>
<td>Ann Danoff MD</td>
<td>NY Harbor VAMC Acting Director and Program Director</td>
</tr>
<tr>
<td></td>
<td>Divison of Endocrinology</td>
</tr>
<tr>
<td></td>
<td>NYU School of Medicine</td>
</tr>
<tr>
<td></td>
<td>423 East 23rd Street New York NY 10010</td>
</tr>
<tr>
<td>James Felicetta MD</td>
<td>Phoenix VAMC</td>
</tr>
<tr>
<td></td>
<td>650 E. Indian School Road</td>
</tr>
<tr>
<td></td>
<td>Phoenix AZ 85012</td>
</tr>
<tr>
<td>Hermes Florez MD</td>
<td>Miami VAMC</td>
</tr>
<tr>
<td></td>
<td>VAMC Miami (151) 1201 NW 16th Street</td>
</tr>
<tr>
<td></td>
<td>Miami FL 33125</td>
</tr>
<tr>
<td>Moti Kashyap MD</td>
<td>Long Beach VA Healthcare System</td>
</tr>
<tr>
<td></td>
<td>5901 E. 7th Street (111-1111)</td>
</tr>
<tr>
<td></td>
<td>Long Beach CA 90822</td>
</tr>
<tr>
<td>Michael Krastins MD</td>
<td>Albany VAMC VAMC 111L</td>
</tr>
<tr>
<td></td>
<td>113 Holland Ave.</td>
</tr>
<tr>
<td></td>
<td>Albany NY 12208</td>
</tr>
<tr>
<td>John Leidy MD</td>
<td>Huntington WV VAMC</td>
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<td>Research Service (131)</td>
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<tr>
<td></td>
<td>1540 Spring Valley Dr.</td>
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<td>Huntington WV 25704</td>
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<tr>
<td>James Levenson MD</td>
<td>Boston VAMC</td>
</tr>
<tr>
<td></td>
<td>Research Service (151-MAV)</td>
</tr>
<tr>
<td></td>
<td>150 So. Huntington Ave</td>
</tr>
<tr>
<td></td>
<td>Boston MA02130</td>
</tr>
<tr>
<td>Samer Nakhle MD</td>
<td>Las Vegas VAMC</td>
</tr>
<tr>
<td></td>
<td>Southern Nevada VA Healthcare System</td>
</tr>
<tr>
<td></td>
<td>P.O. Box 360001</td>
</tr>
<tr>
<td></td>
<td>North Las Vegas NV 89036</td>
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532
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Site Address</th>
</tr>
</thead>
</table>
| Sylvette Nazario MD      | San Juan VAMC  
Research Service 151  
10 Casia St.  
San Juan PR 00921-3201 |
| Amy O'Donnell MD         | Buffalo VAMC  
3495 Bailey Ave.  
Research Service (151)  
Buffalo NY14215         |
| Suzanne Quinn MD         | Gainesville VAMC  
1601 SW Archer Rd (111)  
Gainesville FL 32608    |
| Lynetta Skoretz MD       | Loma Linda VA HCS Clinical Research Center (151-ORC)  
11201 Benton Street, Room 4D-19  
Loma Linda CA 92357     |
| Udho Thadani MD          | Oklahoma City VAMC  
920 Stanton L. Young Blvd. WP3120  
Oklahoma City OK 73104  |
| Theodor Theodoropoulos MD| Bay Pines VAMC  
10000 Bay Pines Blvd.  
Bldg. 100, 4D-136  
Bay Pines FL 33744       |
| Thomas Wiegmann MD       | Kansas City VAMC  
4801 E. Linwood Blvd.  
Research Service 151  
Kansas City MO 64128     |
The following information concerning ________________________________, who participated as a clinical investigator in the submitted study ________________________________ is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME
Anthony H. Cincotta, PhD

TITLE
President

FIRM/ORGANIZATION
VeroScience LLC

SIGNATURE

DATE
04/13/2008

Paperwork Reduction Act Statement
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857
April 13, 2008

RE:
DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

was a site Investigator for the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1) and is
and would be compensated for
such services.

Neither he nor anyone else had access to unblinded study data from the Cycloset Safety Trial before they were
analyzed in accordance with the pre-specified Statistical Analysis Plan for the study. All study data were held in
blinded fashion by the study data management organization until
several months after the final subject had exited the trial, all study queries by the sponsor were
completed, and the database had been locked. No one, including the sponsor, had access to unblinded data until
after the primary and secondary analyses of the Statistical Analysis Plan had been executed by

Anthony H. Cincotta, PhD
President
DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning ____________, who participated as a clinical investigator in the submitted study ____________ is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☑ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual’s disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME
Anthony H. Cincotta, PhD

TITLE
President

FIRM/ORGANIZATION
VeroScience LLC

SIGNATURE

DATE
04/13/2008

Paperwork Reduction Act Statement

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Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857
April 13, 2008

RE:
DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Was a

for the Cycloset Safety Trial (Study No. 165-AD-04-03- US-1) at the initiation of the study by its previous sponsor, PLIVA d.d. in July of 2004. The study was fully enrolled on December 31, 2005. VeroScience acquired the Cycloset NDA from PLIVA d.d. on May 16, of 2006. Consequently:

b(6)

b(6)

Neither he nor anyone else had access to unblinded study data from the Cycloset Safety Trial before they were analyzed in accordance with the pre-specified Statistical Analysis Plan for the study. All study data were held in blinded fashion by the study data management organization until several months after the final subject had exited the trial, all study queries by the sponsor were completed, and the database had been locked. No one, including the sponsor, had access to unblinded data until after the primary and secondary analyses of the Statistical Analysis Plan had been executed by:

b(4)

b(4)

Anthony H. Cincotta, PhD

President
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>20-866</th>
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<tr>
<td>Proprietary Name:</td>
<td>Cycloset</td>
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<tr>
<td>Established/Proper Name:</td>
<td>bromocriptine mesylate</td>
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<tr>
<td>Dosage Form:</td>
<td>Tablets</td>
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<td>RPM:</td>
<td>Lena Weber, 301-796-1306</td>
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<td>Division:</td>
<td>DMEP</td>
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### NDAs:

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<th>Type</th>
<th>505(b)(1)</th>
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<tbody>
<tr>
<td>Description</td>
<td>A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.</td>
</tr>
</tbody>
</table>

### 505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

- [ ] If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

- [ ] No changes
- [ ] Updated

Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

### Actions

- Proposed action: AP

### Promotional Materials (accelerated approvals only)

Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/oder/guidance/2197db.pdf). If not submitted, explain N/A

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<tr>
<th>Action Goal Date</th>
<th>October 15, 2008</th>
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<tr>
<td>Action Goal Date (if different)</td>
<td>May 5, 2009</td>
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<td>Promotional Materials</td>
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版: 2008-09-23

The Application Information section is (only) a checklist. The Contents of Action Package section (beginning on page 5) lists the documents to be included in the Action Package.
<table>
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<th>Application Characteristics</th>
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<tr>
<td><strong>Review priority:</strong> Standard</td>
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<tr>
<td>- [ ] Fast Track</td>
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<tr>
<td>- [ ] Rolling Review</td>
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<td>- [ ] Orphan drug designation</td>
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<tr>
<td>- [ ] Rx-to-OTC full switch</td>
</tr>
<tr>
<td>- [ ] Rx-to-OTC partial switch</td>
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<tr>
<td>- [ ] Direct-to-OTC</td>
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<tr>
<td><strong>NDAs:</strong> Subpart H</td>
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<td>- [ ] Accelerated approval (21 CFR 314.510)</td>
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<td>- [ ] Restricted distribution (21 CFR 314.520)</td>
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<td><strong>BLAs:</strong> Subpart E</td>
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<tr>
<td>- [ ] Accelerated approval (21 CFR 601.41)</td>
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<td>- [ ] Restricted distribution (21 CFR 601.42)</td>
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<tr>
<td><strong>Subpart I</strong></td>
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<tr>
<td>- [ ] Approval based on animal studies</td>
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<td><strong>Comments:</strong></td>
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<th>Date reviewed by PeRC (required for approvals only)</th>
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<td>If PeRC review not necessary, explain: _______</td>
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<tr>
<th>BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)</th>
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<th>BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)</th>
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<th>Public communications (approvals only)</th>
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<tr>
<td>- Office of Executive Programs (OEP) liaison has been notified of action</td>
</tr>
<tr>
<td>- Press Office notified of action (by OEP)</td>
</tr>
<tr>
<td>- Indicate what types (if any) of information dissemination are anticipated</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
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</table>
| X HHS Press Release
FDA Talk Paper
CDER Q&A's
Other |

---

2 All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

Version: 9/5/08
### Exclusivity

<table>
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<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>Is approval of this application blocked by any type of exclusivity?</td>
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</tr>
<tr>
<td>NDAs and BLAs: Is there existing orphan drug exclusivity for the “same”</td>
<td>No</td>
</tr>
<tr>
<td>drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</td>
<td></td>
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<tr>
<td>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar</td>
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<tr>
<td>effective approval of a 505(b)(2) application? (Note that, even if</td>
<td></td>
</tr>
<tr>
<td>exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</td>
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<tr>
<td>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar</td>
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<td>effective approval of a 505(b)(2) application? (Note that, even if</td>
<td></td>
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<tr>
<td>exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</td>
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<td>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that</td>
<td>N/A</td>
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<tr>
<td>would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</td>
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<tr>
<td>NDAs only: Is this a single enantiomer that falls under the 10-year</td>
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<tr>
<td>approval limitation of 505(u)? (Note that, even if the 10-year approval</td>
<td></td>
</tr>
<tr>
<td>limitation period has not expired, the application may be tentatively</td>
<td></td>
</tr>
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<td>approved if it is otherwise ready for approval.)</td>
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### Patent Information (NDAs only)

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>Patent Information: Verify that form FDA-3542a was submitted for patents</td>
<td>Verified</td>
</tr>
<tr>
<td>that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</td>
<td></td>
</tr>
<tr>
<td>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</td>
<td>N/A</td>
</tr>
<tr>
<td>[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</td>
<td>N/A No paragraph III certification</td>
</tr>
<tr>
<td>[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</td>
<td>N/A (no paragraph IV certification)</td>
</tr>
</tbody>
</table>
[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner’s receipt of the applicant’s notice of certification?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If “No,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “Yes,” a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.

**CONTENTS OF ACTION PACKAGE**

- Copy of this Action Package Checklist³

**Official Approvals List**

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) Included

- Documentation of consent/non-consent by officers/employees Included

- Copies of all action letters (including approval letter with final labeling) AP 5/05/09
  AE 10/15/99
  NA 11/20/98

**Labeling**

- Package Insert (write submission/communication date at upper right of first page of PI)
  - Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 4/29/09
  - Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 5/1/09 (PI, PCI)
  - Original applicant-proposed labeling 12/26/08 (carton/container)
  - Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable N/A
  - Medication Guide/Package Insert/Instructions for Use (write submission/communication date at upper right of first page of each piece) Patient Counseling Insert
    - Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 5/1/09
    - Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 5/1/09

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08
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<th>Category</th>
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<td>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</td>
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<tr>
<td>Most-recent division proposal for (only if generated after latest applicant submission)</td>
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<tr>
<td>Most recent applicant-proposed labeling</td>
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<td>Labeling reviews (indicate dates of reviews and meetings)</td>
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<td>Proprietary Name</td>
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<td>Internal memoranda, telecons, etc.</td>
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</table>

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

Version: 9/5/08
### Minutes of Meetings

- PeRC (indicate date; approvals only) 1/28/09
- Pre-Approval Safety Conference (indicate date; approvals only) Not applicable
- Regulatory Briefing (indicate date) No mtg
- Pre-NDA/BLA meeting (indicate date) No mtg
- EOP2 meeting (indicate date) No mtg
- Other (e.g., EOP2s, CMC pilot programs) None

### Advisory Committee Meeting(s)

- Date(s) of Meeting(s) None
- 48-hour alert or minutes, if available None

### Office Director Decisional Memo (indicate date for each review)

None

### Division Director Summary Review (indicate date for each review)

5/05/09

### Cross-Discipline Team Leader Review (indicate date for each review)

None

### Clinical Reviews

- Clinical Team Leader Review(s) (indicate date for each review) 3/25/09
- Clinical review(s) (indicate date for each review) 1/16/09
- Social scientist review(s) (if OTC drug) (indicate date for each review) N/A

### Safety update review(s) (indicate location/date if incorporated into another review)

1/16/09 (MOR)

### Financial Disclosure review(s) or location/date if addressed in another review OR

1/16/09

### Clinical reviews from other clinical areas/divisions/Centers (indicate date of each review)

12/1/08 (CBER, Bruce Schneider, M.D.).

### Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)

NN

### Risk Management

- Review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) None
- REMS Memo (indicate date)
- REMS Document and Supporting Statement (indicate date(s) of submission(s))

### DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)

11/19, 1/12/09

### Clinical Microbiology Team Leader Review(s) (indicate date for each review)

N/A

### Clinical Microbiology Review(s) (indicate date for each review)

N/A

---

*Filing reviews should be filed with the discipline reviews.*

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<td>• CMC/product quality review(s) (indicate date for each review)</td>
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Version: 9/5/08
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<td>Facilities Review/Inspection</td>
<td>Date completed: May 2008</td>
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<td>- TBP-EER</td>
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Version: 9/5/08
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
5/5/2009 01:23:33 PM
May 1, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Cycloset Label Revision and FDA Information Request Letter of 05/01/09
Amendment 49

Dear Dr. Parks,

Reference is made to an information request letter (herewith attached) received from FDA on May 1, 2009 requesting VeroScience to conduct two clinical trials with Cycloset in subjects with type 2 diabetes to determine its efficacy in improving glycemic control in these studies as follows:

1) A 6-month, double-blind, controlled clinical trial evaluating Cycloset as add-on to Thiazolidinediones therapy.

2) A 6-month, double-blind, controlled clinical trial evaluating Cycloset as add-on to insulin therapy.

Reference is also made to the latest FDA revision to the Cycloset package insert that was received via email from our project manager, Jena Weber on April 27, 2009 (herewith attached).

Reference is also made to a phone call request from Jena Weber on May 1, 2009 to delineate the timelines for the Pediatric Studies Plan for Cycloset in the Treatment of Type 2 Diabetes.

We acknowledge FDA’s request to study Cycloset as add-on to thiazolidinediones and also as add-on to insulin in patients with type 2 diabetes and we intend to pursue the design and conduct of such studies. This submission contains the protocol synopses for each of the above mentioned Cycloset efficacy trials, including dates of study initiation, study completion and study report submission to FDA. This submission also contains our latest version of the Cycloset package insert that incorporates all of the latest FDA revisions to it. Finally, we also include in this submission, an updated table of the timelines for the conduct of the pediatric studies for Cycloset treatment of type 2 diabetes previously submitted to FDA in amendment 42 (December 2008).

FDA Form 356h and the above referenced emails follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
INFORMATION REQUEST LETTER

VeroScience, LLC
Attention: Anthony Cincotta, Ph.D.
President and CSO
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your August 22, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate) 0.8 mg tablets.

We also refer to your submission dated April 13, 2008, which constituted a complete response to our October 15, 1999, action letter.

We have the following comments and information requests.

A considerable subset of patients with type 2 diabetes mellitus use a thiazolidinedione or insulin for glycemic control. As previously communicated, there is limited information supporting the efficacy of Cycloset in these settings based on the data submitted to date. Therefore, we strongly encourage you to conduct the following two clinical trials in the near future:

1. A 6-month, double-blind, controlled clinical trial evaluating Cycloset as add-on to thiazolidinedione therapy.

2. A 6-month, double-blind, controlled clinical trial evaluating Cycloset as add-on to insulin therapy.

Please respond to this letter in writing. Include your rationale if you are not planning to conduct such trials.

If you are planning to conduct such trials, include in your response the anticipated timeframe for initiating these trials. You may include a set of questions at the time of protocol submission if there are specific aspects of the protocols for which you are seeking input from the Division.
If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at
301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
5/1/2009 08:28:42 AM
April 13, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Cycloset Label Revision – Accepted FDA revisions
Amendment 48

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, on April 8, 2009 requesting our revision of the Cycloset label per FDA recommendations attached thereto. We have accepted and incorporated all the FDA recommendations to the label and this submission contains our latest such version of the Cycloset label and our responses to certain FDA comments made on the last version of the Cycloset label.

We acknowledge FDA’s request in the latest Cycloset label revision for postmarketing commitments to study Cycloset as add-on to thiazolidinediones and also as add-on to insulin in patients with type 2 diabetes and we intend to pursue the design and conduct of such studies.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
April 13, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Cycloset Label Revision – Accepted FDA revisions
Amendment 48

Dear Dr. Parks,

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FDA Form 356h and the above referenced emails from Dr. Miabin follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
Document room update the following:

N 020866 N 000 AZ 13-Apr-2008 31-Mar-2009

Document Type: Forms
Form Group: CONSULT
Form Name: OSE Consult Request
Submission Description: Tradename Request #4

Author(s)/Discipline(s)
1. Jena Weber, CSO

Signer(s)
1. Jena Weber

Please re-evaluate ASAP. Last DMEPA review found tradename acceptable (12/19/08). 90-day AC period has expired.

Supervisory Signer(s)
1. Jena Weber

Please re-evaluate ASAP. Last DMEPA review found tradename acceptable (12/19/08). 90-day AC period has expired.
REQUEST FOR CONSULTATION

TO (Division/Office): USE
  t. Cheryl Campbell

FROM: DMEP
  Jena Weber, PM

DATE 3/30/09
IND NO. NDA NO. 20-866
TYPE OF DOCUMENT Tradename Proposal
DATE OF DOCUMENT 4/13/08

NAME OF DRUG Bromocriptine mesylate
PRIORITY CONSIDERATION S
CLASSIFICATION OF DRUG Anti-diabetic
DESIRED COMPLETION DATE 4/10/09

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE-NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVIEION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMATIVE REVIEW
☐ OTHER (SPECIFY BELOW): Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH
☐ TYPE A OR B NDA REVIEW
☐ END OF PHASE II MEETING
☐ CONTROLLED STUDIES
☐ PROTOCOL REVIEW
☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH
☐ CHEMISTRY REVIEW
☐ PHARMACOLOGY
☐ BIOPHARMACEUTICS
☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILITY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Approvable letter for this NDA issued on 10/15/1999; tradename "Cycloset," was acceptable. Also reference your review from December 18, 2008, (OSE-RCM 2008-1940); tradename found acceptable. Please re-evaluate as 90-day period has expired. DMEP plans to take an action (AP) by April 15th, 2009. All labeling is available via EDR.

NAME AND PHONE NUMBER OF REQUESTER
  Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
  ☑ DFS ONLY
  ☑ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
3/31/2009 09:41:26 AM
Please re-evaluate ASAP. Last DMEPA review found tradename acceptable (12/19/08). 90-day AC period has expired.
Proposed PROPRIETARY Name: Cycloset
Proposed ESTABLISHED Name: bromocriptine mesylate

Sound-alike/Look-alike Names of CONCERN ONLY (See worksheet on page 2):

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</table>

DDMAC RECOMMENDATION: X Acceptable Unacceptable

Comments/Concerns:

Sauers
SIGNATURE OF DDMAC REPRESENTATIVE 03.19.09 DATE

SAFETY EVALUATOR RECOMMENDATION: ~ Unacceptable ~ Acceptable

Comments/Concerns:
Weber, Jena M

From: Aljaburi, Lina
Sent: Tuesday, March 17, 2009 3:38 PM
To: Parks, Mary H; Joffe, Hylton
Cc: Weber, Jena M
Subject: FW: Cycloset/NDA 20-866

Attachments: Cycloset NC.doc

We've got clearance from DMEPA for the Cycloset name for another 90 days!

Thanks,
Lina

From: Wright, Mildred
Sent: Tuesday, March 17, 2009 3:18 PM
To: Aljaburi, Lina; Weber, Jena M
Subject: Cycloset/NDA 20-866

Lina/Jena,
Name good to go.
Millie

Cycloset NC.doc (40 KB)
March 10, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Submission of previously emailed information for Cycloset Safety Trial Amendment 47

Dear Dr. Parks,

Reference is made to several emails (herewith attached) received from our FDA medical reviewer of the Cycloset NDA, Dr. Robert Misbin, requesting additional information and analyses from the Cycloset Safety Trial (Study number 165-AD-04-03-US-1) database. We have previously responded to these requests via email to Dr. Misbin and are now also officially submitting these responses to the Cycloset NDA 20-866 in this submission. This submission contains:

1. January 5, 2009 email to Dr. Misbin with attachment of analyses of table of baseline concomitant diabetes and cardiovascular medications among subjects with a CVD SAE in the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1)
2. January 8, 2009 email to Dr. Misbin with attachment of summary write-up on the baseline diabetes and cardio-protective medications at baseline among subjects in the Cycloset Safety Trial.
3. January 9, 2009 email to Dr. Misbin with attachment of information regarding relation between baseline history of strokes or coronary revascularization surgery and CVD event occurrence in the Cycloset Safety Trial.
4. January 20, 2009 email to Dr. Misbin with attachment of information regarding subjects experiencing an adverse event of hypotension or orthostatic hypotension during the Cycloset Safety Trial.
5. March 4, 2009 email to Dr. Misbin with attachment of information on an analysis of the relation between cardio-protective medications at baseline among subjects in the Cycloset Safety Trial and between group differences in the percent of subjects having a CVD endpoint event.
6. A summary table from the above submissions on at baseline and from baseline concomitant diabetes and cardiovascular medications among subjects in the Cycloset Safety Trial.

FDA Form 356h and the above referenced emails from Dr. Misbin follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony.Cincotta@VeroScience.com.

Sincerely,

[Signature]

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

Page 1 of 1
FYI

From: Wright, Mildred
Sent: Tuesday, March 10, 2009 4:45 PM
To: Aljuburi, Lina
Cc: Campbell, Cheryl; Wright, Mildred
Subject: RE: Trade name review for NDA 20-866 Cycloset

We will re-open. Won't need a new consult.
Millie

From: Aljuburi, Lina
Sent: Tuesday, March 10, 2009 1:54 PM
To: Wright, Mildred
Cc: Campbell, Cheryl; Weber, Jena M
Subject: Trade name review for NDA 20-866 Cycloset

Hi Millie,

We have the following application:

**"YA 20-866
  trade name: Cycloset
  generic name: bromocriptine

DMEPA completed a review on December 18, 2008 (signed off 12/19/08), stating the trade name "Cycloset" is acceptable. We have yet to take an action (for oh so many reasons ;) and realize that we will not be making the cut-off of 90-days prior to the trade name being found acceptable. So we need DMEPA to do the abbreviated review they do in these cases.

The OSE RCM # is 2008-1940

Melina Griffis' review is attached here for your reference.

<< File: Cycloset_TradeNameReview.pdf >>
Do you need another consult - or can you reopen the old one?

Feel free to contact me for whatever additional information you need to complete this request.

Many thanks,
Lina

Lina Aljuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
l.aljuburi@fda.hhs.gov
301-796-1188 (phone)
301-796-9712 (fax)
March 3, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Cycloset PI and PPI revisions
Amendment 46

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, on February 20, 2009 containing the FDA’s most current revisions to the Cycloset Package Insert (PI) and Patient Package Insert (PPI). We have reviewed these revisions and accepted the vast majority of the FDA suggested changes to the Cycloset PI and PPI. This submission includes a) our updated version of the Cycloset PI and PPI taking these latest FDA recommendations into account and b) our responses to FDA’s comments and queries regarding the PI (this document addresses the rationale for those particular instances in the current label revision where we either provided additional text other than that suggested by the Agency or provided responses to questions raised in the comments posted in the label by the Agency that were not fully self explanatory in the revised label itself).

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies as well as a CD that contains the entire contents of this submission. This CD was scanned by Symantec Antivirus Program 10.1.0.394 Scan engine 81.3.0.13 Virus Definition File 3/2/2009 rev.2 and found to be virus-free. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
Thanks - so the only outstanding issues are my memo and labeling. After I finish the AC stuff I'll wrap up my memo.

Hylton

Okay. We can take an action.

Yep, happens all the time, especially when pending NAI. Of course, there might be times when it's not NAI (or minor stuff) and you would want ot discuss the findings with DSI . . . .

Lee

Can you advise me here? Can we take an action for Cycloset with just the inspection summary signed off in DFS and a "pending - interim NAI" for one site?

Thanks.

Mary,

Roy called me this afternoon to discuss the outstanding clinical inspection regarding Dr. Barencoots. Bottom line is that DSI does not know when they may have the individual report finalized. Roy said that this has never been a problem before with our Division or other review divisions. He referred me to the inspection summary signed off in DFS (by Roy and his team leader) on January 12, 2009. The final inspection classification states "pending - interim NAI," for Dr. Barencoorts; the 2 other reports on Drs. Littlejohn and Fisher were designated "VAI." Let me know how you would like to proceed; we can phone Roy tomorrow if you like.

Thanks,

Jena
They need to finalize their report in DFS.

FYI, Mary — we've been trying to get this written DSI report for weeks, if not months, but it hasn't happened yet.

DSI said that the inspection was acceptable even though it hasn't officially been written up. Do we need an official report or is an email saying that it is acceptable good enough? I thought we needed all reviews in DFS before we can take an action but wasn't sure if we've been applying that rule to something like this.

Hilton

FYI, See below.

Jena

Thanks for the reminder. My understanding is that it has been sent to me, but I don't have it yet. Please let me know if this will be a problem for you with taking an action.

Roy

Roy,

Just checking in to see if a final written report was issued on Elena Barengolta, M.D. We are getting very close to taking an action on this submission.

thanks,

Jena

Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306
February 16, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to FDA DMEP Questions
Amendment 45

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, on February 9, 2009 requesting responses to questions posed by Dr. Hylton Joffe regarding data from the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1). This submission provides the requested responses to those questions.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
REQUEST FOR CONSULTATION

TO (Division/Office): DDMAC
Att. Sam Skariah

FROM: DMEP
Jena Weber, PM

DATE: 1/30/09
IND NO.
NDA NO. 20-866

TYPE OF DOCUMENT: PI/PPI
DATE OF DOCUMENT: 1/21/09

NAME OF DRUG: Bromocriptine mesylate
PRIORITY CONSIDERATION: S

CLASSIFICATION OF DRUG: Anti-diabetic
DESIRABLE COMPLETION DATE: 2/9/09

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE-nda MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☒ OTHER (SPECIFY BELOW). PP/PPI

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH
☐ TYPE A OR B NDA REVIEW
☐ END OF PHASE II MEETING
☐ CONTROLLED STUDIES
☐ PROTOCOL REVIEW
☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

☐ CHEMISTRY REVIEW
☐ PHARMACOLOGY
☐ BIOPHARMACEUTICS
☒ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILITY STUDIES
☐ PHASE IV STUDIES

☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☒ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is the current label submitted by VeroScience for Cycloset. It includes our first round suggested revisions. Please review and comment as appropriate. I will include you in the final labeling meeting. We plan to take an action (AP) in 7 – 10 days.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☒ DFS ONLY
☒ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER
19 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

__________________________
Jena Weber
1/30/2009 03:39:57 PM
NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-866  Supplement #  Efficacy Supplement Type SE-

Proprietary Name: Cycloset
Established Name: bromoscriptine mesylate tablets
Strengths: 0.8 mg
Applicant: VeroScience Inc.
Agent for Applicant: N/A

Date of Application: April 13, 2008
Date of Receipt: April 15, 2008
Date clock started after UN: Date of Filing Meeting: June 4, 2008
Filing Date: June 15, 2008
Action Goal Date (optional): User Fee Goal Date: October 15, 2008

Indication requested: CYCLOSET is indicated as an adjunct to diet and exercise to improve glycemic control (hyperglycemia) in patients with type 2 diabetes mellitus (type 2 diabetes).

CYCLOSET is indicated as:
- Monotherapy in addition to diet and exercise.
- Adjunctive therapy in patients with type 2 diabetes mellitus who are failing therapy with insulin secretagogues (e.g. sulfonylureas) or metformin alone or another oral agent to improve glycemic control.
- Combination therapy with insulin if insulin alone does not provide adequate glycemic control.

Type of Original NDA: (b)(1) X (b)(2) □
AND (if applicable)
Type of Supplement: (b)(1) □ (b)(2) □

NOTE: If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid □ Exempt (orphan, government) □ Waived (e.g., small business, public health) X

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b).

Version 6/14/2006
Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant’s proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? NO
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? NO
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? NO

- Does the submission contain an accurate comprehensive index? NO
  If no, explain:

- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA NO

2. This application is an eNDA or combined paper + eNDA YES
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format X CTD format ☐
   Combined NDA and CTD formats

Does the eNDA, follow the guidance? (http://www.fda.gov/cder/guidance/2353fni.pdf) YES

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format? All.

Additional comments: Appropriate paper signatures obtained.
3. This application is an eCTD NDA.  
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be  
   electronically signed.

   Additional comments: — Noted and acknowledged.

   • Patent information submitted on form FDA 3542a?  
     YES

   • Exclusivity requested?  
     NO
     NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is  
     not required.

   • Correctly worded Debarment Certification included with authorized signature?  YES
     If foreign applicant, both the applicant and the U.S. Agent must sign this certification.

     NOTE: Debarment Certification should use wording in FD&C Act section 306(b)(1) i.e.,  
     "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of  
     any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection  
     with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

   • Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric  
     studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?  YES

   • If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the  
     application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and  
     (B)?  YES

   • Is this submission a partial or complete response to a pediatric Written Request?  NO

     If yes, contact PMHT in the OND-IO

   • Financial Disclosure forms included with authorized signature?  YES
     (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an  
     agent.)
     NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

   • Field Copy Certification (that it is a true copy of the CMC technical section)  YES

   • PDUFMA and Action Goal dates correct in tracking system?  YES
     If not, have the document room staff correct them immediately. These are the dates EES uses for  
     calculating inspection dates.

   • Drug name and applicant name correct in COMIS?  If not, have the Document Room make the  
     corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not  
     already entered.

   • List referenced IND numbers:  34,661

   • Are the trade, established/proper, and applicant names correct in COMIS?  YES
     If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) ____________________________ NO
  If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) ____________________________ NO
  If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) ____________________________ NO
  If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES
  If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES
  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? YES
- Risk Management Plan consulted to OSE/IO? YES
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? N/A

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? N/A

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment? YES
  If EA submitted, consulted to EA officer, OPS? YES

- Establishment Evaluation Request (EER) submitted to DMPQ? YES

- If a parenteral product, consulted to Microbiology Team? N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 4, 2008

NDA 20-866

DRUG NAME: Cycloset (bromocriptine mesylate) tablets 0.8 mg

APPLICANT: VeroScience Inc.

BACKGROUND: NDA was submitted August 1997; an approvable letter was issued October 15, 1999. The company provided a complete response on April 13, 2008.

ATTENDEES: Drs. Joffe, Misbin, Pian, Sahlroot, Kuijpers, Choe, Vaidyanathan, Ysern, and Ms. Weber

ASSIGNED REVIEWERS (including those not present at filing meeting): Biswas, Blay, Carothers, Vishwanathan, Griffis, Lewin.

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Reviewer</th>
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<td>Medical:</td>
<td>Joffe/Misbin</td>
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<td>Aljabouri/Weber</td>
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<td>Other Consults:</td>
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Per reviewers, are all parts in English or English translation? YES
If no, explain:

Version 6/14/2006
CLINICAL

- Clinical site audit(s) needed?
  If no, explain: YES
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY N/A

STATISTICS FILE

BIOPHARMACEUTICS FILE

- Biopharm. study site audits(s) needed? YES

PHARMACOLOGY/TOX FILE

- GLP audit needed? NO

CHEMISTRY FILE X REFUSE TO FILE

- Establishment(s) ready for inspection? YES
- Sterile product? NO
  If yes, was microbiology consulted for validation of sterilization? N/A

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

Application poorly assembled, difficult to locate files, data, forms, etc.

☐ No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

Version 6/14/2006
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. X Convey document filing issues/no filing issues to applicant by Day 74.

Jena M. Weber
Regulatory Project Manager
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
1/29/2009 02:16:19 PM
CSO
January 21, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 — Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jens Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Latest Revision to Cycloset Label
Amendment 44

Dear Dr. Parks,

Reference is made to an email (hereewith attached) received from our FDA project manager, Jens Weber, on January 8, 2009 requesting revisions to the latest version of the Cycloset label. This submission includes 1) the VeroScience revisions to the Cycloset label a) in final format, b) with FDA accepted changes highlighted, and c) with FDA accepted changes and VeroScience changes highlighted and 2) VeroScience responses to FDA comments to the Cycloset label where such responses were required or appropriate.

FDA Form 356h and the above referenced email from Jens Weber follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony.Cincotta@VeroScience.com.

Sincerely,

[Signature]

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
CLINICAL INSPECTION SUMMARY

DATE: January 12, 2009

TO: Jena Weber, Regulatory Project Manager
    Robert Misbin, M.D., Medical Officer
    Division of Metabolism and Endocrinology Products

FROM: Roy Blay, Ph.D.
      Good Clinical Practice Branch 1
      Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
         Branch Chief
         Good Clinical Practice Branch 1
         Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 20-866

APPLICANT: VeroScience,

DRUG: Cycloset (bromocriptine mesylate) tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Type 2 diabetics with adjunct Cycloset therapy to determine whether there is a lessening in the number of serious adverse events as compared to placebo

CONSULTATION REQUEST DATE: August 13, 2008

DIVISION ACTION GOAL DATE: October 1, 2008

PDUFA DATE: October 15, 2008
I. BACKGROUND:

The conduct of protocol #165-AD-04-03-US-1, entitled “A Randomized, Double-Blind, Placebo-Controlled Trial to Assess Safety and Tolerability during Treatment of Type 2 Diabetes with Usual Diabetes Therapy and Either Cycloset® or Placebo” was inspected.

The sites of Drs. Littlejohn, Fischer, and Barengolts were selected on the basis of the enrollment of large numbers of study subjects.

The primary objective of this study was to determine whether adjunct therapy of Type 2 diabetics with Cycloset® would lessen the number of serious adverse events as compared to placebo.

II. RESULTS (by Site):

<table>
<thead>
<tr>
<th>Name of CI, Location</th>
<th>Protocol #:/ # of Subjects/</th>
<th>Inspection Dates</th>
<th>Final Classification</th>
</tr>
</thead>
</table>
| Thomas Littlejohn, M.D.  
Piedmont Medical Research, 1901 S. Hawthorne Road, Suite 306  
Winston-Salem, NC 27103 | 165-AD-04-03-US-1/152/ | 6-10 Oct 2008 | NAI |
| Jerome Fischer, M.D.  
DGD Research Inc.  
803 Castrovilla Road, Suite 140  
San Antonio, TX 78237 | 165-AD-04-03-US-1/81/ | 2-14 Oct 2008 | VAI |
| Elena Barengolts, M.D.  
Chicago Westside VAMC  
CHCS Westside  
820 S. Damen Ave.  
M/C111  

Key to Classifications:
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

1. Thomas Littlejohn, M.D.  
Piedmont Medical Research, 1901 S. Hawthorne Road, Suite 306  
Winston-Salem, NC 27103

   a. What was inspected: 175 subjects were screened for the study, 152 were randomized, 85 completed the study, and 67 were dropped after enrollment because of protocol violations and adverse events. The study records for 16 subjects were reviewed in-depth and compared against source documents. Consent forms were present for all subjects. Medical histories, laboratory
reports, adverse event, concomitant medication, and drug accountability reporting were reviewed.

b. General observations/commentary: Review of the records noted above revealed no significant discrepancies/regulatory violations.

c. Assessment of data integrity: Data appear acceptable in support of the respective application.

2. Jerome Fischer
   DGD Research Inc.
   803 Castroville Road, Suite 140
   San Antonio, TX 78237

   a. What was inspected: 131 subjects were screened for the study, 81 were enrolled, 50 were screen failures, and 33 completed the study. The study records for 31 subjects were reviewed in-depth, and signed consent forms were present for all reviewed subject records. Adverse event, concomitant medication, and drug accountability reporting were reviewed. Source documents were compared with the corresponding CRFs and the data listings accompanying the assignment.

   b. General observations/commentary: Subject 03980 was dispensed placebo in error rather than the study drug.

   c. Assessment of data integrity: Data appear acceptable in support of the respective application; however, the review division should consider the impact, if any, of the data regarding subject 03980 receiving placebo.

3. Elena Barengolts, M.D.
   Chicago Westside VAMC
   CHCS Westside
   820 S. Damien Ave.
   M/C111
   Chicago, IL 60654

   a. What was inspected: 212 subjects were screened for the study, 136 were randomized, and 76 completed the study. The study records for the 136 randomized subjects were reviewed and compared against source documents. Consent forms, medical histories, laboratory reports, glycosylated hemoglobin values (HgbA1c) levels, adverse events, concomitant medications, intercurrent illnesses, and drug accountability reporting were reviewed.

   b. General observations/commentary: Review of the records noted above revealed no significant discrepancies/regulatory violations.
c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

Observations noted above are based on the draft inspection report received from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

**III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Receipt and review of the EIR for Dr. Barengolt's site is pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be any observations of clinical and regulatory significance discovered after reviewing the EIR.

The data generated by the clinical sites of Drs. Barengolt, Littlejohn and Fischer appear acceptable in support of the respective application; however, the review division should consider the impact, if any, of the data from Dr. Fischer's site regarding subject 03980 receiving placebo.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

**CONCURRENCE:**

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Roy Blay
1/12/2009 02:15:08 PM
CSO

Constance Lewin
1/12/2009 02:29:13 PM
MEDICAL OFFICER
**REQUEST FOR CONSULTATION**

**TO (Division/Office):**
OSE
Att. Cheryl Campbell

**FROM:**
DMEP
Jena Weber, PM

<table>
<thead>
<tr>
<th>DATE</th>
<th>IND NO.</th>
<th>NDA NO.</th>
<th>TYPE OF DOCUMENT</th>
<th>DATE OF DOCUMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/9/09</td>
<td></td>
<td>20-866</td>
<td></td>
<td>12/26/08</td>
</tr>
</tbody>
</table>

**NAME OF DRUG:**
Bromocriptine mesylate

**PRIORITY CONSIDERATION:**
S

**CLASSIFICATION OF DRUG:**
Anti-diabetic

**NAME OF FIRM:**
VeroScience, LLC

**DATE OF DOCUMENT:**
1/26/09

**REASON FOR REQUEST**

### I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE-nda MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

### II. BIOMETRICS

#### STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

#### STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

### IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

### V. SCIENTIFIC INVESTIGATIONS

- CLINICAL

- PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**
Response to FDA labeling (from OSE) comments on carton/containers. See attachment.

**NAME AND PHONE NUMBER OF REQUESTER**
Jena Weber, 301-796-1306

**METHOD OF DELIVERY (Check one)**
- DFS ONLY

**SIGNATURE OF RECIPIENT**

**SIGNATURE OF DELIVERER**
December 26, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Issues and Questions for Cycloset Label
Amendment 41

Dear Dr. Parks,

Reference is made to several emails (herewith attached) received from FDA during the past few weeks requesting more information on the Cycloset NDA 20-866. Firstly, we received emails from Dr. Robert Misbin of DMEP of December 15 and 16, 2008 requesting information on a) certain psychiatric disorders adverse events for all subjects and b) a narrative of an adverse event – pulmonary fibrosis for a single subject occurring during the Cycloset Safety Trial (study no. 165-AD-04-03-US-1). Secondly, we received other emails from our FDA project manager, Jena Weber, of December 17 and 23, 2008 requesting a) changes to the Cycloset container and carton labels requested by OSE and b) information regarding 1) the Cycloset Pediatric Study Plan and 2) certain analyses of cardiovascular serious adverse events in the Cycloset Safety Trial. This submission provides responses to all those email requests. This submission contains 1) the requested data on psychiatric disorders in the Cycloset Safety Trial submitted via email to Dr. Misbin on December 17, 2008, 2) The requested changes to the Cycloset Pediatric Study Plan, 3) The requested data on baseline concomitant diabetes and cardiovascular disease medications as well as history of ischemic heart disease among subjects in the Cycloset Safety Trial and 4) the requested changes to the container and carton labels for Cycloset by OSE.

FDA Form 356h and the above referenced emails from Jena Weber and Dr. Misbin follow this letter. We are providing an original (blue) archival copy, a clinical (tan) copy, and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
Section 4

Changes to Cycloset Container and Carton Labels
Changes to Cycloset Container and Carton Labels

as Requested by OSE via Email of December 17, 2008

(attached hereto)
6 Page(s) Withheld

___ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

___ Draft Labeling (b5)

___ Deliberative Process (b5)
From: Weber, Jena M [mailto:jenaweb@fda.hhs.gov]
Sent: Wednesday, December 17, 2008 9:35 AM
To: Anthony Cincotta
Subject: See attached
Importance: High

Anthony,

Here are the comments that I received from OSE; please address these.

Thanks,
Jena

<<OSE Labeling comments.doc>>

Project Manager
Division of Metabolism & Endocrinology Products
Jena Weber@fda.hhs.gov
301-796-1306

OSE Labeling comments, please address.

We continue to have concerns with the size of the company name and logo on the container labels. As currently displayed the size of the company name and logo, "Veroscience", is of similar size and prominence compared to the proprietary name and strength and should be decreased so that it does not compete with the proprietary and established names and strength. Revise so that the company name and logo is relocated to the bottom of the principle display panel which is a less prominent area.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
1/9/2009 09:47:55 AM
January 5, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Electronic Copy of Amendment 27 - Cycloset Safety Trial Clinical Study Report
Amendment 43

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, of January 5, 2009 requesting an electronic copy of Sections 14 and 16 of the Cycloset Safety Trial Clinical Study Report - Amendment 27 to the Cycloset NDA 20-866. This submission provides an electronic copy of the entire Cycloset Safety Trial Clinical Study Report (Amendment 27 to the Cycloset NDA) inasmuch as Sections 14 and 16 comprise the majority of the Report. A paper copy of the Table of Contents for the Volumes of Amendment 27 as well as for Sections 14 and 16 thereof are included for assistance in reviewing the Amendment.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy containing the CD with the Amendment 27. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony.Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
## REQUEST FOR CONSULTATION

**TO (Division/Office):**
OSE
Att. Cheryl Campbell

**FROM:**
DMEP
Jena Weber, PM

**DATE**
12/5/08

**IND NO.**

**NDA NO.**
20-866

**TYPE OF DOCUMENT**
Tradename Proposal

**DATE OF DOCUMENT**
4/13/08

**NAME OF DRUG**
Bromocriptine mesylate

**PRIORITY CONSIDERATION**
S

**CLASSIFICATION OF DRUG**
Anti-diabetic

**DESIRED COMPLETION DATE**
12/29/08

**NAME OF FIRM:** VeroScience, LLC

### REASON FOR REQUEST

#### I. GENERAL

- [ ] NEW PROTOCOL
- [ ] PROGRESS REPORT
- [ ] NEW CORRESPONDENCE
- [ ] DRUG ADVERTISING
- [ ] ADVERSE REACTION REPORT
- [ ] MANUFACTURING CHANGE/ADDITION
- [ ] MEETING PLANNED BY
- [ ] PRE-nda MEETING
- [ ] END OF PHASE II MEETING
- [ ] RESUBMISSION
- [ ] SAFETY/EFFICACY
- [ ] PAPER nda
- [ ] CONTROL SUPPLEMENT
- [ ] RESPONSE TO DEFICIENCY LETTER
- [ ] FINAL PRINTED LABELING
- [ ] LABELING REVISION
- [ ] ORIGINAL NEW CORRESPONDENCE
- [ ] FORMATIVE REVIEW
- [ ] OTHER (SPECIFY BELOW): Trade name review

#### II. BIOMETRICS

<table>
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<tr>
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#### III. BIOPHARMACEUTICS

- [ ] DISSOLUTION
- [ ] BIOAVAILABILITY STUDIES
- [ ] PHASE IV STUDIES
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- [ ] PROTOCOL-BIOPHARMACEUTICS
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- [ ] REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- [ ] SUMMARY OF ADVERSE EXPERIENCE
- [ ] POISON RISK ANALYSIS

#### V. SCIENTIFIC INVESTIGATIONS

- [ ] CLINICAL
- [ ] PRECLINICAL

### COMMENTS/SPECIAL INSTRUCTIONS:

**Approvable letter for this NDA issued on 10/15/1999.** At this time, the tradename “Cycloset,” was acceptable. Please evaluate again (3rd time). See consult sent on 5/20/08, when the UFGD was October 15, 2008. **New UFGD is 1/15/09.** All labeling is available via EDR.

**NAME AND PHONE NUMBER OF REQUESTER**
Jena Weber, 301-796-1306

**METHOD OF DELIVERY (Check one)**
- [x] DFS ONLY
- [ ] HAND

**SIGNATURE OF RECEIVER**

**SIGNATURE OF DELIVERER**
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Jena Weber
Jena,

I believe you have copies of the letters sent to Drs. Fischer and Littlejohn. The inspection of Dr. Barengolts was completed and the inspector told me that there were no observations resulting from the inspection. I have not yet received the inspection report but anticipate that it will be an NAI classification. I will also be working on the inspection summary for you.

Please let me know if you need any other information at this time.

Roy

---

Roy,

Looks like we just have 1 outstanding review from DSI on the Cycloset NDA. We are planning to take an action (AP) on/before Jan. 13th. Please let me know when to expect this.

Thanks,

Jena

Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306
NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-866  Supplement #  Efficacy Supplement Type  SE-

Proprietary Name: Cycloset
Established Name: bromocriptine mesylate tablets
Strengths: 0.8 mg
Applicant: VeroScience Inc.
Agent for Applicant: N/A

Date of Application: April 13, 2008
Date of Receipt: April 15, 2008
Date clock started after UN: 
Date of Filing Meeting: June 4, 2008
Filing Date: June 15, 2008
Action Goal Date (optional): 
User Fee Goal Date: October 15, 2008

Indication requested: CYCLOSET is indicated as an adjunct to diet and exercise to improve glycemic control (hyperglycemia) in patients with type 2 diabetes mellitus (type 2 diabetes). CYCLOSET is indicated as:
- Monotherapy in addition to diet and exercise.
- Adjunctive therapy in patients with type 2 diabetes mellitus who are failing therapy with insulin secretagogues (e.g. sulfonylurea) or metformin alone or another oral agent to improve glycemic control.
- Combination therapy with insulin if insulin alone does not provide adequate glycemic control.

Type of Original NDA: AND (if applicable) (b)(1) X (b)(2) 
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) X

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b).

Version 6/14/2006
Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? NO
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? NO
  If yes, explain:

- If yes, has OCD/DMPQ been notified of the submission? NO

- Does the submission contain an accurate comprehensive index? NO
  If no, explain:

- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA NO

2. This application is an eNDA or combined paper + eNDA YES
   This application is: All electronic □ Combined paper + eNDA □
   This application is in: NDA format □ CTD format □
   Combined NDA and CTD formats X

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2335fnl.pdf) YES

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format? All.

   Additional comments: Appropriate paper signatures obtained.

Version 6/14/2006
3. This application is an eCTD NDA. 
   NO
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be 
electronically signed.

   Additional comments: – Noted and acknowledged.

- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? --- Years NO

   NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is 
   not required.

- Correctly worded Debarment Certification included with authorized signature? YES
   If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

   NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., 
   “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of 
   any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection 
   with this application.” Applicant may not use wording such as “To the best of my knowledge . . . .”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric 
  studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the 
  application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and 
  (B)? YES

- Is this submission a partial or complete response to a pediatric Written Request? NO

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an 
  agent.)

   NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES

- PDUFA and Action Goal dates correct in tracking system? YES
  If not, have the document room staff correct them immediately. These are the dates EES uses for 
  calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the 
  corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not 
  already entered.

- List referenced IND numbers: 34,661

- Are the trade, established/proper, and applicant names correct in COMIS? YES
  If no, have the Document Room make the corrections.

Version 6/14/2006
• End-of-Phase 2 Meeting(s)? Date(s) __________________________ NO
  If yes, distribute minutes before filing meeting.

• Pre-NDA Meeting(s)? Date(s) __________________________ NO
  If yes, distribute minutes before filing meeting.

• Any SPA agreements? Date(s) __________________________ NO
  If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

• If Rx, was electronic Content of Labeling submitted in SPL format? YES
  If no, request in 74-day letter.

• If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES

  If no, explain. Was a waiver or deferral requested before the application was received or in the
  submission? If before, what is the status of the request:

• If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to
  DDMAC? YES

• If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES

• If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? YES

• Risk Management Plan consulted to OSE/IO? YES

• If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for
  scheduling submitted? NA

**If Rx-to-OTC Switch or OTC application:**

• Proprietary name, all OTC labeling/packaging, and current approved PI consulted to
  OSE/DMETS? YES

• If the application was received by a clinical review division, has
  DNPCE been notified of the OTC switch application? Or, if received by
  DNPCE, has the clinical review division been notified? N/A

**Clinical**

• If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Version 6/14/2006
Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment? YES
  If EA submitted, consulted to EA officer, OPS? YES

- Establishment Evaluation Request (EER) submitted to DMPQ? YES

- If a parenteral product, consulted to Microbiology Team? N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 4, 2008

NDA 20-866

DRUG NAME: Cycloset (bromocriptine mesylate) tablets 0.8 mg

APPLICANT: VeroScience Inc.

BACKGROUND: NDA was submitted August 1997; an approvable letter was issued October 15, 1999. The company provided a complete response on April 13, 2008.

ATTENDEES: Drs. Joffe, Misbin, Pian, Sahlroot, Kuijpers, Choe, Vaidyanathan, Ysern, and Ms. Weber

ASSIGNED REVIEWERS (including those not present at filing meeting): Biswas, Blay, Carothers, Vishwanathan, Griffis, Lewin.

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Reviewer</th>
</tr>
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<td>Medical:</td>
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<td>Davis-Bruno/Kuijpers</td>
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<td>Chemistry:</td>
<td>Al-Hakim/Ysern</td>
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<tr>
<td>Environmental Assessment (if needed):</td>
<td>NN</td>
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<td>Biopharmaceutical:</td>
<td>Choe/Vaidyanathan</td>
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<td>Microbiology, sterility:</td>
<td>NN</td>
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<tr>
<td>Microbiology, clinical (for antimicrobial products only):</td>
<td>NN</td>
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<tr>
<td>DSI:</td>
<td>CLN, BPH (Blay, Vishwanathan)</td>
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<td>OPS:</td>
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<td>Aljuburi/Weber</td>
</tr>
<tr>
<td>Other Consults:</td>
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</tbody>
</table>

Per reviewers, are all parts in English or English translation? YES

If no, explain:

Version 6/14/2006
CLINICAL

- Clinical site audit(s) needed? YES
  If no, explain:
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY N/A

STATISTICS FILE

BIOPHARMACEUTICS FILE

- Biopharm. study site audits(s) needed? YES

PHARMACOLOGY/TOX FILE

- GLP audit needed? NO

CHEMISTRY FILE X REFUSE TO FILE

- Establishment(s) ready for inspection? YES
- Sterile product? NO
  If yes, was microbiology consulted for validation of sterilization? N/A

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
Application poorly assembled, difficult to locate files, data, forms, etc.

X No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

Version 6/14/2006
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Jena M. Weber  
Regulatory Project Manager
Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

1. it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,

2. it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or

3. it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean any reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

1. The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

2. No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,

3. All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

1. Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the
original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s Office of Regulatory Policy representative.
Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)?
   YES ☐ NO ☐

   /\"No,\" skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #s:

3. Is this application for a drug that is an \"old\" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
   YES ☐ NO ☐

   /\"Yes,\" skip to question 7.

4. Is this application for a recombinant or biologically-derived product?
   YES ☐ NO ☐

   /\"Yes \"contact your ODE\'s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
       YES ☐ NO ☐

   \textit{(Pharmaceutical equivalents} are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; \textit{and} (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   /\"No,\" to (a) skip to question 6. Otherwise, answer part (b and (c)).

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
       YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?
       YES ☐ NO ☐

   /\"Yes,\" (c), list the pharmaceutical equivalent(s) and proceed to question 6.

   If \"No,\" to (c) list the pharmaceutical equivalent and contact your ODE\'s Office of Regulatory Policy representative.

   Pharmaceutical equivalent(s):

Version 6/14/2006
6. (a) Is there a pharmaceutical alternative(s) already approved? YES(NO)

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and c).

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES(NO)

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES(NO)

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES(NO)

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES(NO)

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES(NO)

11. Is the application for a duplicate of a listed drug whose only difference is YES(NO)
that the rate at which the product’s active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)?
   (This is different from the patent declaration submitted on form FDA 3542 and 3542a.)
   YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

   ☐ Not applicable (e.g., solely based on published literature. See question #7

   ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
   Patent number(s):

   ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
   Patent number(s):

   ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
   Patent number(s):

   ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
   Patent number(s):

   **NOTE:** IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

   ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
   Patent number(s):

   ☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
   Patent number(s):


   ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
   Patent number(s):

Version 6/14/2006
14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.  
  YES ☐ NO ☐

  If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug.

  Was this listed drug product(s) referenced by the applicant? (see question # 2)  
  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?
  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

  YES ☐ NO ☐

If "Yes," please list:

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<th>Product No.</th>
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Version 6/14/2006
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
12/29/2008 10:10:21 AM
CSO
Response to Email Request from Hylton Joffe of December 22, 1008 (attached hereto)

I. Rationale for Deferral Request

Product name: Bromocriptine-Quick Release (Cycloset)
IND/NDA/BLA number (as applicable): NDA 20-866
Applicant: VeroScience
Indications(s): Type 2 Diabetes

(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. What pediatric age group(s) are included in your deferral request? Age > 10 < 16 years
2. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
   ✓ (a) Adult studies completed and ready for approval
      (b) Additional postmarketing safety data needed (describe)
      (c) Nature and extent of pediatric data needed (explain)
      (d) Evidence provided of technological problems with development of a pediatric formulation
      (e) Difficulty in enrolling pediatric patients (provide documentation)
      (f) Other (specify)

3. What pediatric age group(s) is/are not included in your deferral request? Ages 0 - 9
4. Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):
   (a) Adequate pediatric labeling exists
   (b) Studies completed in the specified age group
   ✓ (c) Requesting a waiver
   (d) Currently conducting pediatric studies that will be submitted with application
   (e) Other (specify)

5. Has a pediatric plan been submitted to the Agency?
   ☐ If so, provide date submitted.
   ✓ If not, provide projected date pediatric plan is to be submitted.
      The anticipated time for the submission of the pediatric plan is within of approval of Cycloset for the treatment of Type 2 diabetes in an adult patient population.

6. Suggested deferred date for submission of studies.

   The anticipated time of the submission of the studies will be within of the marketing approval of Cycloset for the treatment of type 2 diabetes in an adult (>16 years of age) patient population.

7. Applicant certification. Richard Scranton MD MPH, Chief Medical Officer, VeroScience
Page(s) Withheld

✓ Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)
REQUEST FOR CONSULTATION

TO (Division/Office):
OSE
Att. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE: 12/18/08
IND NO. 20-866
NDA NO.
TYPE OF DOCUMENT
DATE OF DOCUMENT 4/13/08

NAME OF DRUG: Bromocriptine mesylate
PRIORITY CONSIDERATION S
CLASSIFICATION OF DRUG Anti-diabetic
DESIRED COMPLETION DATE 1/05/09

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL
- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE-nda MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS
- STATISTICAL EVALUATION BRANCH
- TYPE A OR B NDA REVIEW
- END OF PHASE III MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):
- STATISTICAL APPLICATION BRANCH
- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS
- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE
- PHASE IV SURVEILLANCE/EPIEDEMOLOGY PROTOCOL
- DRUG USE e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS
- CLINICAL
- PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Approvable letter issued on 10/15/1999. Re-submission dated April 13, 2008. Please conduct post-marketing search for neuropsych events (events of special approach) - crude counting and data mining for bromocriptine mesylate, and evaluate as a safety review, not RMP.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
- DFS ONLY

SIGNATURE OF RECEIVER
SIGNATURE OF DELIVERER
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Jena Weber
12/19/2008 01:53:49 PM
REQUEST FOR CONSULTATION

TO (Division/Office):
OSE
Att. Cheryl Campbell

FROM:
DMEP
Jena Weber, PM

DATE: 12/5/08
IND NO.
NDA NO.
20-866
TYPE OF DOCUMENT:
Trademark Proposal
DATE OF DOCUMENT:
4/13/08

NAME OF DRUG:
Bromocriptine mesylate
PRIORITY CONSIDERATION:
S
CLASSIFICATION OF DRUG:
Anti-diabetic
DESIRE COMPLETION DATE:
12/29/08

NAME OF FIRM:
VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE-NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER (SPECIFY BELOW): Trade name review

II. BIOMETRICS

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III. BIOPHARMACEUTICS

☐ DILUTION
☐ BIOAVAILABILITY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
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☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Approvable letter for this NDA issued on 10/15/1999. At this time, the tradename "Cycloset," was acceptable. Please evaluate again (3rd time). See consult sent on 5/20/08, when the UFGD was October 15, 2008. New UFGD is 1/15/09. All labeling is available via EDR.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☐ DPD'S ONLY
☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-----------------------
Jena Weber
November 24, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Issues and Questions for Cycloset Label
Amendment 41

Dear Dr. Parks,

Reference is made to an email (herewith attached) from our FDA project manager, Jena Weber, of November 6, 2008 requesting labeling changes and responses to FDA issues and questions regarding the Cycloset Label. This submission provides responses to that email request. This submission contains 1) the FDA letter specifying issues and questions of our draft Cycloset label with our responses to those issues and questions and related attachments thereto, 2) the revised, per FDA request, annotated label for Cycloset, and 3) the revised, per FDA request, un-annotated label for Cycloset.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a clinical (tan) copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
Dear Jena,

I have completed my review of the inspection report for Dr. Fischer. It is a minor VAI, and the letter is currently under review by my supervisor (you'll get a copy of the letter as soon she signs off on the letter in DFS).

I am continuing to wait for the inspection report for Dr. Littlejohn. Again, a Form 483 was not issued, and it will probably be an NAI.

I have again requested an update of the inspection for Dr. Barengotts and am awaiting a response.

For the moment, the inspections have revealed nothing problematic. Should that change, I will alert you immediately. Please feel free to ask for updates as you need them.

Thanks for keeping in touch on this NDA.

Roy

---

From: Weber, Jena M
Sent: Wednesday, November 19, 2008 9:48 AM
To: Blay, Roy A
Cc: Misbin, Robert I
Subject: Cycloset - NDA 20-866

Roy,

n you please update me on the status of the clinical inspections for Cycloset.

Thanks,
Jena

Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306
November 12, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Clinical and Container Label Requests
Amendment 40

Dear Dr. Parks,

Reference is made to 1) an email (herewith attached) from Dr. Misbin on November 7, 2008 requesting information on the concomitant diabetes medication changes for subjects during the Cycloset Safety Trial (Study Number 165-AD-04-03-US-1) and to 2) another email (herewith attached) from our project manager, Jena Weber, requesting copies of the carton and container labels for Cycloset. This submission provides responses to both of these email requests.

FDA Form 356h follows this letter. We are providing an original (blue) archival copy, a clinical (tan) copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony N. Cincotta, PhD
President and Chief Scientific Officer
# REQUEST FOR CONSULTATION

**TO (Division/Office):**
SE
Attn. Cheryl Campbell

**FROM:**
DMEP
Jena Weber, PM

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<td>Labeling (PI, PPI, carton &amp; container)</td>
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<td>Anti-diabetic</td>
<td>11/15/08</td>
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**NAME OF FIRM:** VeroScience, LLC

## REASON FOR REQUEST

### I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY

- PRE-NDMEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT

- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMATIVE REVIEW
- OTHER (SPECIFY BELOW): Labeling re-submission

### II. BIOMETRICS

**STATISTICAL EVALUATION BRANCH**
- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW): 

**STATISTICAL APPLICATION BRANCH**
- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW): 

### III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

### IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPEIDEMIOLOGY PROTOCOL
- DRUG USE & P POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

### V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:** Reference our DR letter sent 10/8/08, as per recommendations from OSE. Company has responded; please review and comment prn on all proposed LBL. Each section (PI, PPI, carton & container) is available via EDR dated 10/9/08.

**NAME AND PHONE NUMBER OF REQUESTER:**
Jena Weber, 301-796-1306

**METHOD OF DELIVERY (Check one):**
- [ ] DOLY
- [X] HAND

**SIGNATURE OF RECEIVER**

**SIGNATURE OF DELIVERER**
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
10/14/2008 12:15:15 PM
October 9, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to chemistry request for information on Cycloset stability data and analytical methods Amendment 39

Dear Dr. Parks,

Reference is made to a phone call from Dr. Xavier Ysern, the FDA chemist reviewing our Cycloset NDA, on October 8, 2008. Dr. Ysern requested that we submit to the NDA a) stability data for the Cycloset drug product manufactured by PLIVA d.d. in Zagreb, Croatia and utilized in the Cycloset Safety Trial (study number 165-AD-04-03-US-1), b) recent stability data from at least one registration batch of Cycloset drug product manufactured by the proposed commercial manufacturer of Cycloset, Patheon Inc. for comparison to the PLIVA product stability data and c) information on the comparison of analytical methods historically used for analysis, identification and determination of bromocriptine and related compounds. We are herewith providing this information to the Chemistry section of NDA 20-866 in this submission as Amendment 39 to this NDA.

FDA Form 356h follows this letter. We are providing an original (blue) archival copy, a (red) chemistry copy, and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

[Signature]

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
October 9, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to DMEPA Instruction for Container Label and Package Insert Modifications
Amendment 38

Dear Dr. Parks,

Reference is made to the email communication from FDA to VeroScience on October 8, 2008 and its attached Discipline Review Letter (included herein) regarding DMEPA instructions for modifications to the Cycloset container labels and package insert. We have addressed the DMEPA instructions for modifications to the Cycloset label and package insert in this Amendment 38 to NDA 20-866. The modified package insert per DMEPA instruction is included in this submission as both a WORD document and in SPL format and both are electronic submissions on a single disc. We have also included these package insert modifications as a paper submission. Finally, we have made the changes to the retail and physician container labels as instructed and these new labels are submitted in paper form and also electronically on the same disc with the modified package insert.

FDA Form 356h and the above referenced email communication from FDA follow this letter. The enclosed information disk was scanned with Symantec AntiVirus Version 10.1.0.3594 Scan Engine 81.2.0.23 Virus Definition File Version 10/9/2008 rev 3 and found to be virus-free. We are providing an original (blue) archival copy, a (tan) clinical copy, and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony.Cincotta@VeroScience.com.

Sincerely,

[Signature]

Anthony Cincotta, PhD
President and Chief Scientific Officer
October 8, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Pediatric Partial Waiver and Deferral for Cycloset in the Treatment of Type 2 Diabetes
Amendment 36

Dear Dr. Parks,

Reference is made to the attached email communication to VeroScience from FDA dated July 23, 2008 wherein FDA requested the submission of either a pediatric drug development plan or a request for pediatric waiver/deferral for Cycloset use in the treatment of type 2 diabetes in children/adolescents. This Amendment 36 is submitted to comply with the Pediatric Research Equity Act (Public Law 108-155) (PREA) following the recommendations in the FDA Guidance for Industry - draft guidance of September 2005 on How to Comply with the Pediatric Research Equity Act. We are herein requesting a partial waiver of the requirement to submit pediatric assessments for Cycloset in the treatment of type 2 diabetes with respect to infants and children ages _______ years and a deferral of the requirement to submit pediatric assessments for Cycloset in the treatment of type 2 diabetes with respect to adolescents ages _______ years. The justification and rationale for submitting such a partial waiver/deferral request are succinctly delineated within this submission utilizing the query- answer format recommended and supplied in the aforementioned draft guidance.

We are providing an original (blue) archival copy, a clinical (tan) copy and three desk (black) copies for FDA. Form 356h and a copy of the above referenced FDA - VeroScience email communication follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
I. Rationale for Deferral Request

Product name: Bromocriptine (Cycloset) b(4)
IND/NDA/BLA number (as applicable): NDA 20-866
Applicant: VeroScience
Indications(s): Type 2 Diabetes
(Note: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. What pediatric age group(s) are included in your deferral request? Age > 10 < 18 years
2. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
   ✓ (a) Adult studies completed and ready for approval
   (b) Additional postmarketing safety data needed (describe)
   (c) Nature and extent of pediatric data needed (explain)
   (d) Evidence provided of technological problems with development of a pediatric formulation
   (e) Difficulty in enrolling pediatric patients (provide documentation)
   (f) Other (specify)
3. What pediatric age group(s) is/are not included in your deferral request? Ages 0 - 10
4. Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):
   (a) Adequate pediatric labeling exists
   (b) Studies completed in the specified age group
   ✓ (c) Requesting a waiver
   (d) Currently conducting pediatric studies that will be submitted with application
   (e) Other (specify)
5. Has a pediatric plan been submitted to the Agency?
   □ If so, provide date submitted.
   ✓ If not, provide projected date pediatric plan is to be submitted.
   The anticipated time for the submission of the pediatric plan is —— b(4)
   Approval of Cycloset for the treatment of Type 2 diabetes in an adult patient population.
6. Suggested deferred date for submission of studies.

The anticipated time of the submission of the studies will be —— b(4)
years of the marketing approval of Cycloset for the treatment of type 2 diabetes in an adult (>18 years of age) patient population.

7. Applicant certification.

Richard Scranton MD MPH, Chief Medical Officer
VeroScience
Page(s) Withheld

✓ Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)
Product name: Bromocriptine ———— (Cycloset) h(4)
IND/NDA/BLA number (as applicable): NDA 20-866
Applicant: VeroScience
Indications(s): Type 2 Diabetes

1. Identify pediatric age group(s) included in your waiver request.
   Waiver request for Infants and children aged ———— h(4)

2. With regard to each age group for which a waiver is sought, state the reason(s) for
   waiving pediatric assessment requirements with reference to applicable statutory
   authority (i.e., one of the options (a)-(d) listed below — choose all that apply):

✓ (a) Studies are impossible or highly impractical (because the number of
   Pediatric patients in this age group are very small to non-existent). If applicable,
   please check from the following list of adult-related conditions that may qualify the
   drug product for disease-specific waivers:

- Age-related macular degeneration
- Alzheimer’s disease
- Arteriosclerosis
- Infertility
- Amyotrophic lateral sclerosis
- Menopause symptoms
- Osteoarthritis
- Parkinson’s disease
X Other (please state and justify)
Type 2 Diabetes – adult onset diabetes mellitus

- Basal cell and squamous cell cancer
- Breast cancer
- Colorectal cancer
- Endometrial cancer
- Hairy cell cancer
- Lung cancer (small cell and non-small cell)
- Oropharynx cancers (squamous cell)
- Ovarian cancer (non-germ cell)
- Pancreatic cancer
- Prostate cancer
- Renal cell cancer
- Uterine cancer

(b) The product would be ineffective or unsafe in one or more of the pediatric age
   group(s) for which a waiver is being requested.
(c) The product fails to represent a meaningful therapeutic benefit over existing therapies
   for pediatric patients and is unlikely to be used in a substantial number of all pediatric
   age groups or the pediatric age group(s) for which a waiver is being requested.
(d) Reasonable attempts to produce a pediatric formulation for one or more of the
   pediatric age group(s) for which the waiver is being requested have failed. Please
   document previous attempts to make a pediatric formulation and describe reasons for
   failure.
3. Provide evidence that the statutory reason(s) for waiver of pediatric studies have been met (not necessary if a 2(a) category is checked).

Justification for Pediatric waiver for children aged 10-18

Only recently has type 2 diabetes become a reality for children aged 10-18 years. The US SEARCH study (population based study of diabetes in children across six centers) identified 6379 children or adolescents with any type of diabetes from ~3.5 million youth. In this study, among younger children with diabetes, ≥80% were type 1 diabetics in contrast to older youth where the proportion of diabetic children with type 2 diabetes ranged from 6% in non-Hispanic whites to 76% in American Indians. According to the American Academy of Pediatrics, in 2001 the prevalence of type 2 diabetes cases per 1000 youth in all age groups from birth to age 19 was 0.22. The highest prevalence was among American Indian youths aged 10-19 at 1.74 per 1000. The Academy states that this was the largest surveillance effort on diabetes in youth at the time.¹

Although the incidence of type 2 diabetes appears to be on the rise, the absolute number of youth with type 2 diabetes is still very small. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are currently recruiting children 10-17 years of age for the TODAY study. Less than 500 subjects have been recruited since May 2004. The study hopes to enroll a total of 750 subjects in time to publish results by 2011.² This study confirms the focus on children aged >10 where the prevalence of type 2 diabetes is increasing. The ADA consensus statement of 2000 supports this approach as evident by the following statement “Currently, children with type 2 diabetes are usually diagnosed over the age of 10 years and are in middle to late puberty. As the childhood population becomes increasingly overweight, type 2 diabetes may be expected to occur in younger prepubertal children.” Although epidemiology studies of the prevalence of type 2 diabetes in children are limited, the available evidence suggests that the incidence is for the most part nearly non-existent for children under the age of 10 years (see table 1).

² http://www.cdc.gov/diabetes/registert/cdp2.htm
³ ClinicalTrials.gov NCT00081328
Since the prevalence of type 2 diabetes in children is still relatively small in comparison to the adult population, studies of pharmacological interventions for the treatment of type 2 diabetes in an adolescent population are limited primarily to children over the age of 10 years. There was however a study of 285 subjects that compared the efficacy and safety of glimepiride or metformin in children with type 2 diabetes mellitus (T2DM) (age 8-17 years). The primary endpoint was mean change in HbA1c from baseline to week 24 and safety was assessed by incidence of hypoglycemia and other adverse events. Subjects with type 2 diabetes and HbA1c between 7.1% and 12.0% were randomized to either glimepiride or metformin for 24 weeks. A total of 78.0% of the glimepiride group and 81.7% of the metformin group completed the study. The authors concluded that glimepiride was safe and effective for use in this population over 24 weeks, but further studies are warranted to determine the best approach to treatment using a combination of diet, exercise and oral anti-hyperglycemic therapy. The study was supported by Sanofi-Aventis, makers of glimepiride and results were published in 2007. \(^4\) Two more recently approved therapies for the treatment of type 2 diabetes have been utilized in investigational studies in children > 10 years of age. For example, exenatide was used in a completed phase 2 study in children aged 10-16 and is also being used in another study that is currently recruiting children with T2DM aged 10-16 years (phase 3). Sitagliptin is being utilized in one ongoing (phase 1) study in patients with T2DM aged 10-17. Currently, there are no investigational studies registered in www.clinicaltrial.gov for children with type 2 diabetes under the age of 10.

Based on our review of current literature and expert opinion, the primary intervention in children (age <10 years) with type 2 diabetes is lifestyle change, including diet and exercise changes. The relatively low (or nearly non-existent) incidence of type 2 diabetes in the pediatric (age <10 years) population coupled with the fact that the primary current recommended treatment modality for the disease is and will continue to be diet and exercise serve as the justification for a partial pediatric waiver for Cycloset for this indication in this subject population.

October 8, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Approvable Letter – Pharmacology and Toxicology Question Response
Amendment 37

Dear Dr. Parks,

At this time we are filing an amendment (Amendment 37) to our pending NDA to resolve an oversight regarding a response to one preclinical question listed in the Approvable Letter issued by the Agency on October 15, 1999.

On April 13, 2008 we filed an amendment (Amendment 29) to provide a Complete Response to all outstanding issues listed in the approvable letter, referenced above. On October 3, 2008, a call was received from Dr. Gemma Kuijpers of FDA requesting further information regarding impurities in the Cycloset drug product. Dr. Kuijpers was informed about where to find the information relating to the impurities in the Cycloset drug product in the original NDA (Volume 4 page 090, Section 4.3.7.1) and in Amendment 29 to the NDA (Volume 3 page 408; Section 4.3.7); however, in reviewing the submission after the telephone call, we have realized that we inadvertently omitted a formal response to Question 4 in the Approvable letter regarding impurities in the drug substance/API. The response should have been provided in Section 5 of Amendment 29. At this time we are correcting that omission.

In the original NDA filing, two impurities were identified in the API produced by

These impurities were identified as Compounds A and B and both were concluded to be brominated
alpha- ergocriptine analogs. Compounds A and B were individually tested to assess mutagenic
potential and were shown to be negative for inducing forward mutations at the TK locus in L51798Y
mouse lymphoma cells under activated and non-activated conditions and these data appear in the
original NDA - nonclinical pharmacology and toxicology section (Volume 7 pages 083-095). These
impurities however, were not found in our studies in the bromocriptine API from

Page 1 of 2
are currently using only——— as a source for bromocriptine API. The Cycloset safety trial used drug product made with only——— and NDA Amendment 29 contains information covering manufacturing of drug product using only——— No drug product is being or will be produced with API from ———— The amounts of impurities in the ———— as listed in the current NDA filing (Amendment 29 to NDA 20-866, Volume 3 pages 010-016; Section 4.2) are ————. Although these impurities are not identified, they are below the ICH limit of 0.1% for qualification.

FDA Form 356h follows this letter and a certification that no ———— will be used for production of Cycloset follows the FDA form. We trust that this amendment will complete the issues related to the preclinical update to our NDA. We are providing an original (blue) archival copy, a yellow (pharmacology/toxicology) copy, a red (chemistry/manufacturing controls) copy and two (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
NDA 20-866                      DISCIPLINE REVIEW LETTER

VeroScience, LLC                      10/8/07
Attention: Anthony Cincotta, Ph.D.
President and CSO
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your April 13, 2008, new drug application (NDA) submitted under section 505(b)
of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate quick
release) Tablets 0.8 mg.

The Division of Medication Error Prevention and Analysis (DMEPA) has completed their review
of your submission, and has the following comments and requests. Please address these in
writing to your NDA file.

Proprietary Name

DMEPA currently has no objections to the use of the proprietary name, Cycloset. DMEPA will
request another review of the proprietary name if approval of the NDA is delayed beyond 90
days from the date of the completed initial review (September 26, 2008) to ensure that there are
no changes in healthcare practices or drug product characteristics that could increase
vulnerability of the proposed name to confusion.

Retail and Physician Container Labels

1. The size of the company name and logo should be decreased so as not to interfere with the
readability of the proprietary name and strength.

2. In accordance with 21 CFR 201.10(g)(2), the prominence of the established name should
be increased to at least ⅔ the size of the proprietary name, and the established name shall
have a prominence commensurate with the prominence with which such proprietary name
or designation appears, taking into account all pertinent factors, including typography,
layout, contrast, and other printing features. We note that in some of the labels, the
established name appears to be of adequate size but in other labels, it does not. Since the
proprietary name for this product is bolded in the labels, the size of the established name
may need to be increased more than ⅔ the size of the proprietary name to satisfy this
requirement.
3. Relocate the net quantity statement to an area on the label that doesn’t intervene with the dosage strength statement (i.e. upper or bottom corner of the principle display panel).

Package Insert

In the Patient Counseling Sections of labeling (sections 2.1, 17.1 and 17.3), patients are instructed to take their morning dose of Cycloset between 8 am and 10 am. Depending on an individual patient’s sleeping patterns, listing specific times for dose administration could create confusion for the patient and lead to possible missed doses. The specific time to administer the dose should be omitted (unless there is a compelling reason not to), and these sections of labeling should be revised to be consistent with the DOSAGE AND ADMINISTRATION section of labeling which states to take the recommended dose of Cycloset within 2 hours after waking in the morning.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

(See appended electronic signature page)

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
10/8/2008 10:59:58 AM
October 6, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Subject Data for Insulin Sensitivity Study (Study Number 1-96-2.2) – Submission of Electronic Copy Amendment 35

Dear Dr. Parks,

Reference is made to the attached email communication to VeroScience from FDA requesting an electronic copy of subject data from the insulin sensitivity study report (Study Number 1-96-2.2) submitted in Amendment 33 to the Cycloset NDA 20-866. We are herewith providing those requested data in electronic format on disc in this Amendment 35 to the NDA. The data tables on disc are in Microsoft Excel application program that can be imported into SAS programs. We note that in Amendment 33, we had inadvertently omitted a re-formatted table of the original data that itself is located within that submission (First Step of the Hyperinsulinemic – Euglycemic Clamp; pages 009 and 013 of Amendment 33) and are including it here in electronic format (Table title in this Amendment 35 submission: Table 3. Cycloset Influence on Insulin Sensitivity: First Step of the Hyperinsulinemic – Euglycemic Clamp).

We are providing an original (blue) archival copy that includes the requested data disc for FDA. This disk was scanned with Symantec Antivirus Version 10.1.0.394 Scan Engine 81.2.0.25 Virus Definition File Version 10/06/2008 rev 6 and found to be virus-free. Form 356h and a copy of the above referenced FDA - VeroScience email communication follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony.Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
September 4, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Outline of Proposed Post-approval Pharmacovigilance Plan for Cycloset for the Treatment of Type 2 Diabetes
Amendment 32

Dear Dr. Parks,

Reference is made to email communications to VeroScience from FDA between the dates of June 6 and August 27, 2008 (attached hereto) regarding the Agency’s instruction for submission of a proposed post-approval pharmacovigilance plan for Cycloset to be included in the Cycloset NDA 20-866. The conclusion of these communications was that VeroScience would submit a detailed outline/overview of a proposed pharmacovigilance plan to be reviewed by the Agency for its possible comments and recommendations that in turn would then be incorporated into a final pharmacovigilance plan for Cycloset by VeroScience and submitted to FDA. This NDA 20-866 Amendment 32 submission provides the FDA-requested detailed outline/overview of the VeroScience proposed pharmacovigilance plan for Cycloset. Of note, this proposed pharmacovigilance plan

We look forward to the Agency’s prompt review of and comments on the enclosed outline of the proposed pharmacovigilance plan so that we may move forward with the final pharmacovigilance safety program submission to FDA as soon as possible.
We are herewith providing an original copy along with 4 additional desk copies of this paper submission. Form 365h and a copy of the above referenced FDA - VeroScience email communications between June 6 and August 27, 2008 follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email me at: Anthony_Cincotta@VeroScience.com.

Sincerely,

[Signature]

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
APPLICATION INFORMATION

NAME OF APPLICANT
VeroScience LLC

DATE OF SUBMISSION
09/04/2008

TELEPHONE NO. (Include Area Code)
401-816-0525

FACSIMILE (FAX) Number (Include Area Code)
401-608-3079

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):
1334 Main Road,
Tiverton, RI 02878

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone number, and FAX number, if applicable)

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)
20-866

ESTABLISHED NAME (e.g., Proper name, USP/NF name)
bromocriptine mesylate

PROPRIETARY NAME (trade name) If ANY
Cycloset

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
(5‘g)-2-Bromo-12‘-hydroxy-2‘-(1-methylethyl)-5‘-(2-methylpropyl)ergotaman-3’,6’,18-trione

CODE NAME (If any)

DOSE FORM
tablet

STRENGTHS:
0.8 mg

ROUTE OF ADMINISTRATION:
oral

(PROPRIETARY) INDICATION(S) FOR USE:
Treatment of Type 2 Diabetes Mellitus

APPLICATION DESCRIPTION

APPLICATION TYPE
(check one)
NEW DRUG APPLICATION (NDA, 21 CFR 314.50)
ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BILOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE
505 (b)(1)
505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION (check one)
ORIGINAL APPLICATION
AMENDMENT TO APENDING APPLICATION
RESUBMISSION

PRESUBMISSION
ANNUAL REPORT
ESTABLISHMENT DESCRIPTION SUPPLEMENT
EFFICACY SUPPLEMENT

LABELING SUPPLEMENT
CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY
CBE
CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION
Submission of Detailed Outline of Proposed Post-approval Pharmacovigilance Plan

PROPOSED MARKETING STATUS (check one)
PRESCRIPTION PRODUCT (Rx)
OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED
1

THIS APPLICATION IS
PAPER
PAPER AND ELECTRONIC
ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMA(s), 510(k)s, IDEs, BUMs, and DMFs referenced in the current application)

IND 34,661
This application contains the following items: (Check all that apply)

- [ ] 1. Index
- [ ] 2. Labelling (check one)  [ ] Draft Labeling  [ ] Final Printed Labeling
- [ ] 3. Summary (21 CFR 314.50 (c))
- [ ] 4. Chemistry section
  - [ ] A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - [ ] B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - [ ] C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- [ ] 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- [ ] 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- [ ] 7. Clinical microbiology (e.g., 21 CFR 314.50(d)(4))
- [ ] 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- [ ] 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- [ ] 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- [ ] 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- [ ] 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- [ ] 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- [ ] 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (v)(2)(A))
- [ ] 15. Establishment description (21 CFR Part 600, if applicable)
- [ ] 17. Field copy certification (21 CFR 314.50 (f)(3))
- [ ] 18. User Fee Cover Sheet (Form FDA 3397)
- [ ] 19. Financial Information (21 CFR Part 54)
- [x] 20. OTHER (Specify) Submission of Detailed Outline of Proposed Post-approval Pharmacovigilance Plan

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT  TYPE OF NAME AND TITLE  DATE

Anthony H. Cincotta, Ph.D., President and CSO  09/04/2008

ADDRESS (Street, City, State, and ZIP Code)  Telephone Number

1334 Main Road, Tiverton, RI 02878  (401) 816-0525

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Food and Drug Administration  Department of Health and Human Services  Food and Drug Administration  Center for Biologics Evaluation and Research (HFM 90)  
Center for Drug Evaluation and Research  1401 Rockville Pike  Rockville, MD 20852-1448  Department of Health and Human Services  Food and Drug Administration  Center for Biologics Evaluation and Research (HFM 90)  
Central Document Room  5501-8 Ammerdale Road  Belleville, NJ 07109-1268  An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Anthony Cincotta

From: Weber, Jena M [jena.weber@fda.hhs.gov]
Sent: Wednesday, August 27, 2008 11:12 AM
To: Anthony Cincotta
Subject: RE: Cycloset

Anthony,

Please submit your draft plan as an amendment to your NDA file. After the clinical and safety reviewers within our Division evaluate it, I will consult OSE for their input. From there, we will determine if a meeting (or t-con) should be scheduled.

Also, in reference to the e-mail that I sent to you yesterday (8/26), please reply in writing to the Cycloset NDA.

Thanks,
Jena

From: Anthony Cincotta [mailto:Anthony_Cincotta@verosciene.com]
Sent: Monday, August 25, 2008 12:07 PM
To: Weber, Jena M
Subject: RE: Cycloset

Dear Jena,

We are now finalizing our detailed overview of our proposed Cycloset Pharmacovigilance Plan for FDA review and I believe we will be submitting it to FDA within a week. Should we submit the overview as an amendment to the NDA or as an FDA communication? Can you give any guidance as to how to proceed from here with this matter?

As mentioned in my previous email communications below, we would like to have a meeting with the appropriate Divisions at FDA to gain their input and guidance on our proposed pharmacovigilance plan before submitting the final full plan. Should we, subsequent to our submission of the overview, make a request for such a meeting to the Division Director, Dr. Parks? Your guidance here would be greatly appreciated.

Regards,
Anthony

From: Weber, Jena M [mailto:jena.weber@fda.hhs.gov]
Sent: Tuesday, June 10, 2008 10:43 AM
To: Anthony Cincotta
Cc: Misin, Robert I
Subject: RE: Cycloset

Sounds good. Please provide draft plan.

Jena
From: Anthony Cincotta [mailto:Anthony_Cincotta@veroscience.com]
Sent: Tuesday, June 10, 2008 10:36 AM
To: Weber, Jena M
Subject: RE: Cycloset

Jena,

Very well. Please let me know if and when we need to submit the Pharmacovigilance Plan draft to initiate a dialogue with FDA on its final format. For now we will await your response from OSE as how to move forward. We were proceeding from the guidances to industry from FDA on this as I mentioned in my last email and can provide a draft Pharmacovigilance Plan within a short period of time from when you instruct us to do so. Is this OK?

Best,
Anthony

From: Weber, Jena M [mailto:jena.weber@fda.hhs.gov]
Sent: Monday, June 09, 2008 2:46 PM
To: Anthony Cincotta
Subject: RE: Cycloset

Thanks for your response. I am sending out consults to the appropriate Divisions that need to be involved in the review of your NDA. I just did not see a specific tab for the RMP, so I wanted to make sure that I was not missing something. I will ask OSE to review what you have submitted and go from there.

Thanks,
Jena

From: Anthony Cincotta [mailto:Anthony_Cincotta@veroscience.com]
Sent: Monday, June 09, 2008 2:16 PM
To: Weber, Jena M
Subject: RE: Cycloset

Jena,

We did not submit a Risk Management Plan (RMP) for the Cycloset NDA with the Complete Response to the approvable letter inasmuch as we are planning to incorporate any relevant aspects of a RMP into our Pharmacovigilance Plan and are expecting input and recommendations from FDA on the construct of this Pharmacovigilance Plan based upon its conclusions on Cycloset safety drawn from data within our Complete Response amendment (#29). The FDA guidances on Development and Use of Risk Minimizing Action Plans (Section VI) and on development of Pharmacovigilance Plans recommend an ongoing dialogue between the Agency and the sponsor to construct an appropriate RMP or Pharmacovigilance Plan. We have every intention of working with the FDA to construct a responsible pharmacovigilance plan for Cycloset, incorporating reasonable elements of design as potentially recommended by the FDA subsequent to its review of the Complete Response. If the division would like to accelerate the dialogue on this matter, we are ready and willing to begin such discussions now. We look to your instruction on the time table and process for doing so.
The Complete Response includes the results from a large (3070 subject), randomized clinical trial on safety of Cycloset, analyses from World Health Organization and FDA pharmacovigilance databases on adverse experiences encountered with the use of the active ingredient in Cycloset, bromocriptine mesylate, dating back over 30 years of its world-wide use, a literature review of any such adverse experiences, and a retrospective analysis of cardiovascular events of subjects within the UK GPRD database exposed to bromocriptine mesylate. The conclusions of the sponsor on the safety and efficacy of Cycloset are delineated in the Overall Summary of Safety and the Overall Summary of Efficacy, respectively, within the Complete Response. Also, the benefit/risk profile of the drug and recommendations for its use are detailed in the Package Insert (Label) for the drug within the amendment. VeroScience has every intent to ensure maximized physician education and awareness of the therapeutic profile for Cycloset for appropriate prescribing of this drug and to ensure earnest efforts to maximize patient safety regarding its use.

Please instruct us on how best to move forward with this aspect of our application review and what steps we can take to facilitate the process (i.e., should we provide a draft of a Pharmacovigilance Plan in the near future prior to meeting with FDA on the matter?).

Best,
Anthony

From: Weber, Jena M [mailto:jena.weber@fda.hhs.gov]
Sent: Friday, June 06, 2008 9:22 AM
To: Anthony Cincotta
Subject: Cycloset

Anthony,

Did you submit a specific Risk Management Plan for the Cycloset NDA, or is it part of Pharmacovigilance?

Thanks,
Jena

Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306
Page(s) Withheld

☐ Trade Secret / Confidential (b4)

☐ Draft Labeling (b4)

☐ Draft Labeling (b5)

☐ Deliberative Process (b5)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
10/1/2008 08:51:40 AM
September 24, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Supplemental Analysis of Primary Safety and Composite Cardiovascular Endpoint from Study No. 165-AD-04-03-US-1 (Cycloset Safety Trial)
Amendment 34

Dear Dr. Parks,

Reference is made to the attached email communications between VeroScience and FDA regarding a supplemental analysis of primary safety and composite cardiovascular endpoint from Study No. 165-AD-04-03-US-1 (Cycloset Safety Trial). In an email to Dr. Misbin at FDA dated July 18, 2008, VeroScience had indicated that it had conducted a supplemental analysis of the primary safety and composite cardiovascular endpoint inclusive of “on-treatment plus off-treatment” subject time during the study period for subjects in the Cycloset Safety Trial and that the results of this analysis recapitulate the findings and conclusions of those presented in the Cycloset Safety Trial Clinical Study Report (Amendment 27 to NDA 20-866). Dr. Misbin indicated that there would be value in submitting this analysis to the NDA and therefore this Amendment 34 to the NDA contains the report of that supplemental analysis. The Appendices for this paper report, including the analytical dataset thereof, are on discs submitted in a separate volume from the paper report. These disks were scanned with Symantec Antivirus Version 10.1.0.394 Scan Engine 81.2.0.25 Virus Definition File Version 9/23/2008 rev 3and found to be virus-free.

Also included in this submission are copies of the tables and figures from Amendments 27 and 29 to this NDA that were recently submitted electronically to Dr. Misbin per his request (see attached email).

We are providing an original (blue) archival copy, a clinical (tan) copy, a statistics (green) copy, and two additional (black) desk copies of this Amendment 34 for FDA. Form 365h and a copy of the above referenced FDA - VeroScience email communications follow this letter. If you have any
questions regarding this submission, please feel free to contact me by phone at 617 966 8413, by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
September 19, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Information Request – Subject Data for Insulin Sensitivity Study (Study Number 1-96-2.2)
Amendment 33

Dear Dr. Parks,

Reference is made to the attached email communication to VeroScience from FDA regarding an Information Request for subject data from the insulin sensitivity study report (Study Number 1-96-2.2) submitted in Amendment 29 (Volume 17) to the Cycloset NDA 20-866. We are herewith providing those requested data in this Amendment 33 to the NDA. These data were originally submitted to FDA under IND 34,661 Annual Report serial number 199 (which contained the entire study report) but they were inadvertently omitted from the NDA filing of this study report in the Amendment 29 NDA submission. For completeness sake, in addition to providing the specific data requests of FDA from this study report, we have also included the original complete data pages from the IND filing of this study report from which the requested data were extracted.

We are providing an original (blue) archival copy, a clinical (tan) copy, a statistics (green) copy, and two additional (black) desk copies for FDA. Form 365h and a copy of the above referenced FDA - VeroScience email communication follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email me at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
September 4, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Outline of Proposed Post-approval Pharmacovigilance Plan for Cycloset for the Treatment of Type 2 Diabetes
Amendment 32

Dear Dr. Parks,

Reference is made to email communications to VeroScience from FDA between the dates of June 6 and August 27, 2008 (attached hereto) regarding the Agency’s instruction for submission of a proposed post-approval pharmacovigilance plan for Cycloset to be included in the Cycloset NDA 20-866. The conclusion of these communications was that VeroScience would submit a detailed outline/overview of a proposed pharmacovigilance plan to be reviewed by the Agency for its possible comments and recommendations that in turn would then be incorporated into a final pharmacovigilance plan for Cycloset by VeroScience and submitted to FDA. This NDA 20-866 Amendment 32 submission provides the FDA-requested detailed outline/overview of the VeroScience proposed pharmacovigilance plan for Cycloset. Of note, this proposed pharmacovigilance plan

[Redacted]

look forward to the Agency’s prompt review of and comments on the enclosed outline of the proposed pharmacovigilance plan so that we may move forward with the final pharmacovigilance safety program submission to FDA as soon as possible.

Page 1 of 2
We are herewith providing an original copy along with 4 additional desk copies of this paper submission. Form 365h and a copy of the above referenced FDA - VeroScience email communications between June 6 and August 27, 2008 follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email me at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
DSI CONSULT: Request for Clinical Inspections

Date: June 10, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
    Joe Salewski, Branch Chief (Acting), GCP2, HFD-47
    Name of DSI Primary Reviewer

Through: Robert Misbin, M.D., Review Division/HFD-510
         Hylton Joffe, M.D. Teamleader, Review Division/HFD-510
         Mary Parks, M.D., Division Director, DMEP

From: Jena Weber, Regulatory Health Project Manager/Division/HFD-510

Subject: Request for Clinical Site Inspections

I. General Information

Application: NDA 20-866
Sponsor: VeroScience, Anthony Cincotta, Ph.D., President, CSO 401-816-0525
Drug: Cycloset (bromocriptine mesylate) Tablets
NME: No
Standard (6-month clock)
Pediatric exclusivity: No

PDUFA: October 15, 2008
Action: October 15, 2008
Inspection Summary Goal Date: October 1, 2008

II. Background Information

Include a brief introduction about the application and include the following:

- New application (re-submission)
- Proposed indication: Type 2 Diabetes Mellitus
- Brief information
  - on drug
  - disease
  - pivotal studies (large clinical trial, Study 165-AD-04-03-US-1)
Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

<table>
<thead>
<tr>
<th>Site # (Name, Address, Phone number, email, fax#)</th>
<th>Protocol #</th>
<th>Number of Subjects</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Site 180, Jerome Fischer DGD Research Inc. 803 Castroville Road, Suite 140 San Antonio, TX 78237</td>
<td>165-AD-04-03-US-1</td>
<td>81</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Site 215, Charles Herring, M.D. New Hanover Medical Research, 1907 Tradd Court, Wilmington, NC 28410</td>
<td>165-AD-04-03-US-1</td>
<td>157</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Site 260, Thomas Littlejohn, M.D., Piedmont Medical Research, 1901 S. Hawthorne Road, Suite 306, Winston-Salem, NC 27103</td>
<td>165-AD-04-03-US-1</td>
<td>152</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Site 350, Sherwyn Schwartz, M.D., DGD Research Inc. 5107 Medical Drive San Antonio, TX 78229</td>
<td>165-AD-04-03-US-1</td>
<td>183</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Site 537, Elena Barengolts, M.D., Chicago Westside VAMC, CHCS Westside, 820 S. Damen Ave., M/C111, Chicago, IL 60654</td>
<td>165-AD-04-03-US-1</td>
<td>136</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
</tbody>
</table>

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Things to consider in decision to submit request for DSI Audit
- Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?
- Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?
- Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?
- Are there concerns that the data may be fraudulent or inconsistent?
Page 3-Request for Clinical Inspections

- Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action
- Expected commonly reported AEs are not reported in the NDA
- Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?
- Is this a new molecular entity?
- Is the data gathered solely from foreign sites?
- Were the NDA studies conducted under an IND?

Rationale for DSI Audits

- A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations
- A specific efficacy concern based on review of site specific efficacy data
- Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results

Domestic Inspections:

Reasons for inspections (please check all that apply):

- X Enrollment of large numbers of study subjects
- ___ High treatment responders (specify):
- ___ Significant primary efficacy results pertinent to decision-making
- ___ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- X ___ Other: Please evaluate 3 out of the 5 investigators specified.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Name of RPM at Ph: 301-796-xxxx or Name of Medical Officer at Ph: 301-796-XXXX.

Concurrence: (as needed)

________________________ Medical Team Leader
________________________ Medical Reviewer
________________________ Director, Division Director (for foreign inspection requests only)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
8/13/2008 02:39:09 PM
VeroScience, LLC
Attention: Anthony H. Cincotta, Ph.D.
President and CSO
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cycloset (bromocriptine mesylate) Tablets.

We also refer to your submission dated April 13, 2008.

We are reviewing the Clinical and Statistical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Additional issues may be identified during the review process, and may be added, deleted, expanded upon, or modified.

1. For the primary safety endpoint and all secondary safety endpoints, we request time-to-event data with censoring variable and a variable for exposure (adjusted person years) for each patient.

2. The datasets should include all randomized patients, not just those patients with events. Demographic and baseline characteristics should be included e.g., treatment group, indicator variables for metformin use, sulfonylurea use, metformin and sulfonylurea use, insulin use, as well as center, VA or non-VA, etc.

3. For the secondary safety endpoint of composite CVD, please provide variables that enable the analysis of individual endpoints in the composite as well as the composite endpoint itself.

4. Due to difficulties in working with the submitted electronic data files, the Statistics team may be requesting more specific and user-friendly datasets in addition to those requested above as the review progresses.
5. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. Please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver/deferral is appropriate. In your request, you should summarize the effects on maturation, reproductive function, behavioral effects etc. that might be expected to occur in children.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call me at 301-796-1306.

Sincerely,

(Signature page appended)

Jena M. Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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Jena Weber
7/23/2008 01:06:00 PM
Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):  Lori Tull, CBER
Center: OTCGT
Division: DCEPT
Mail Code: HF1M-755
Consulting Reviewer Name: Bruce Schneider, M.D.
Building/Room #: WOC 1, 213-S
Phone #: 301-827-8343
Fax #: 
Email Address: Bruce.Schneider@fda.hhs.gov

From (Originating Center): CDER, Jenna Weber
Center: ODS II
Division: DMEP
Mail Code: HFD-510
Requesting Reviewer Name: Robert Misbin, M.D.
Building/Room #: WO, Bld. 22, #3120
Phone#: 301-796-1259
Fax #: 301-796-0712
Email Address: Robert.Misbin@fda.hhs.gov
Requesting Reviewer's Concurring: DFS
Supervisor's Name: DFS

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: July 3, 2008
Requested Completion Date: Sept. 15, 2008
Submission/Application Number: 20-866
Submission Type: RS

Type of Product: Drug-device combination
Drug-biologic combination
Device-biologic combination
Drug-device-biologic combination
Not a combination product X

Submission Receipt Date: April 13, 2008
Official Submission Due Date: April 15, 2008

Name of Product: Cycloset (bromocriptine maleate)
Name of Firm: VeroScience
Intended Use: type 2 DM

Brief Description of Documents Being Provided: Clinical data, 3 volumes for review of Dr. DeFronzo's clamp study.

Documents to be returned to Requesting Reviewer? Yes

Complete description of the request. Approvable letter for this NDA issued on 10/15/1999. As requested by Dr. Misbin, please review and comment on Dr. DeFronzo's clamp study (1-96-2.2). Hard copies to be delivered. UFCD to October 15, 2008.

Type of Request: Consultative Review.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-------------------
Mary Parks
7/8/2008 11:15:34 AM
June 25, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Datasets for Efficacy Analyses from Cycloset Safety Trial – (Report Number 165-AD-04-03-US-1)
Amendment 30

Dear Dr. Parks,

Reference is made to our previous Amendments 27 (the Clinical Study Report for the Cycloset Safety Trial), 28 (the complete data sets for the Cycloset Safety Trial – Clinical Study Report [CSR]), and 29 (The Complete Response to FDA approvable letter to Cycloset for type 2 diabetes) to NDA 20-866: Cycloset™ (Bromocriptine Mesylate) for the treatment of type 2 diabetes submitted on December 12, 2007, March 7, 2008, and April 13, 2008, respectively. This Amendment 30 submission provides the FDA-requested re-formatted efficacy data sets for the Clinical Study Report previously submitted in Amendment 27, contained in Amendment 28 and Summarized in Amendment 29. Subsequent to a teleconference discussion with Dr. Pian of FDA, our statistician for the Cycloset Safety Trial (Study 165-AD-04-03-US-1),1 and myself held on June 5, 2008, we have prepared "datasets specifically tailored for efficacy" respecting Study 165-AD-04-03-US-1, as Dr. Pian has requested and provide them on data disc with this submission.

This submission contains 1 CD data disc containing a) the efficacy datasets from the CSR Report Number165-AD-04-03-US-1 in format requested by Dr. Pian, b) a brief overview of HbA1c efficacy analyses from the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1), and c) copies of efficacy data tables from the CSR for reference. This CD has been scanned and found to be virus-free using Symantec AntiVirus Program: 10.1.0.394 Scan Engine: 81.1.0.13 Virus Definition File 06/24/2008 rev. 3 software.
Form 365h follows this letter. If you have any questions regarding this submission, please feel free to contact me at 617 966 8413 or email me at: Anthony_Cincotta@VeroScience.com

Sincerely,

Anthony Cincotta, PhD
President and Chief Scientific Officer
Date: June 10, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salawski, Branch Chief (Acting), GCP2, HFD-47
Name of DSI Primary Reviewer

Through: Robert Misbin, M.D., Review Division/HFD-510
Hylton Joffe, M.D. Teamleader, Review Division/HFD-510
Mary Parks, M.D., Division Director, DMEP

From: Jena Weber, Regulatory Health Project Manager/Division/HFD-510

Subject: Request for Clinical Site Inspections

I. General Information

Application: NDA 20-866
Sponsor: VeroScience, Anthony Cincotta, Ph.D., President, CSO 401-816-0525
Drug: Cycloset (bromocriptine mesylate) Tablets
NME: No
Standard (6-month clock)
Pediatric exclusivity: No

PDUFA: October 15, 2008
Action: October 15, 2008
Inspection Summary Goal Date: October 1, 2008

II. Background Information

Include a brief introduction about the application and include the following:

- New application (re-submission)
- Proposed indication: Type 2 Diabetes Mellitus
- Brief information
  - on drug
  - disease
  - pivotal studies (large clinical trial, Study 165-AD-04-03-US-1)
Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

<table>
<thead>
<tr>
<th>Site # (Name, Address, Phone number, email, fax#)</th>
<th>Protocol #</th>
<th>Number of Subjects</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 180, Jerome Fischer DGD Research Inc. 803 Castroville Road, Suite 140 San Antonio, TX 78237</td>
<td>165-AD-04-03-US-1</td>
<td>81</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Site 215, Charles Herring, M.D. New Hanover Medical Research, 1907 Tradd Court, Wilmington, NC 28410</td>
<td>165-AD-04-03-US-1</td>
<td>157</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Site 260, Thomas Littlejohn, M.D., Piedmont Medical Research, 1901 S. Hawthorne Road, Suite 306, Winston-Salem, NC 27103</td>
<td>165-AD-04-03-US-1</td>
<td>152</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Site 350, Sherwyn Schwartz, M.D., DGD Research Inc. 5107 Medical Drive San Antonio, TX 78229</td>
<td>165-AD-04-03-US-1</td>
<td>183</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>Site 537, Elena Barendolts, M.D., Chicago Westside VAMC, CHCS Westside, 820 S. Damen Ave., M/C111, Chicago, IL 60654</td>
<td>165-AD-04-03-US-1</td>
<td>136</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
</tbody>
</table>

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Things to consider in decision to submit request for DSI Audit

- Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?
- Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?
- Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?
- Are there concerns that the data may be fraudulent or inconsistent?
Page 3-Request for Clinical Inspections

- Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action
- Expected commonly reported AEs are not reported in the NDA
- Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?
- Is this a new molecular entity?
- Is the data gathered solely from foreign sites?
- Were the NDA studies conducted under an IND?

Rationale for DSI Audits

- A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations
- A specific efficacy concern based on review of site specific efficacy data
- Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results

Domestic Inspections:

Reasons for inspections (please check all that apply):

- [X] Enrollment of large numbers of study subjects
- [ ] High treatment responders (specify):
- [ ] Significant primary efficacy results pertinent to decision-making
- [ ] There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- [X] Other: Please evaluate 3 out of the 5 investigators specified.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Name of RPM at Ph: 301-796-xxxx or Name of Medical Officer at Ph: 301-796-XXXX.

Concurrence: (as needed)

__________________________ Medical Team Leader
__________________________ Medical Reviewer
__________________________ Director, Division Director (for foreign inspection requests only)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
6/12/2008 02:53:18 PM
MEDICAL OFFICER

Hylton Joffe
6/12/2008 04:21:31 PM
MEDICAL OFFICER

Mary Parks
6/13/2008 02:31:00 PM
MEDICAL OFFICER
**DSI CONSULT**

**Request for Biopharmaceutical Inspections**

**DATE:** June 5, 2008

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** Mary Parks, M.D.  
Director, Review Division, HFD-510

**FROM:** Jena Weber, Regulatory Health Project Manager, HFD-510

**SUBJECT:** Request for Biopharmaceutical Inspections  
NDA 20-866  
Cycloset (bromocriptine mesylate) Tablets

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval have been identified for inspection:

<table>
<thead>
<tr>
<th>Study #</th>
<th>Clinical Site (name, address, phone, fax, contact person, if available)</th>
<th>Analytical Site (name, address, phone, fax, contact person, if available)</th>
</tr>
</thead>
</table>
| BON-P6-262 | Algorithmhe Pharma Inc  
1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1  
514-858-6077  
Investigator: Eric Sicard, M.D. | [b(4)] |

**International Inspections:**

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

__X__ There is a lack of domestic data that solely supports approval;
NDA 20-866
Request for Biopharmaceutical Inspection

_____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by September 30, 2008. We intend to issue an action letter on this application by October 15, 2008. This NDA is a resubmission (response to our AE letter dated October 15, 1999), and is on a 6-month review clock.

Should you require any additional information, please contact Ms. Jena Weber at 301-796-1306.

Contact for VeroScience is:
Anthony Cincotta, Ph.D.
1334 Main Road
Tiverton, RI 02878
401-816-0525

Concurrence:
Hylton Joffe, M.D. Medical Team Leader
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
6/6/2008 05:47:31 PM
Jena,

Please see the information below:

<table>
<thead>
<tr>
<th>Study Number</th>
<th>BON-P6-262</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Title</td>
<td>Single Dose Crossover Comparative Bioavailability Study of Bromocriptine Mesylate 0.8 mg Tablets Following Administration of a 4.8 mg Dose in Healthy Male and Female Volunteers / Fed State</td>
</tr>
<tr>
<td>Clinical Site</td>
<td>Algorithmic Pharma Inc., 1200 Beaumont Ave., Mount-Royal, Quebec, Canada, H3P 3P1. Telephone: (514) 858-6077</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Eric Sicard, M.D.</td>
</tr>
</tbody>
</table>

|--------------|--------------------------------------------------|

<table>
<thead>
<tr>
<th>Analytical Site</th>
<th>Name, Address, Phone #</th>
<th>b(4)</th>
</tr>
</thead>
</table>

| Analysis Dates | 08-Nov-2007 to 11-Dec-2007 |

| Analytical Director | |

| Storage Period of Bioanalytic Samples (no. of days from the first day of sample collection to the last day of sample analysis) | 120 days |

Can you also please ask the sponsor the location for the bioanalytical method and validation report?

Thanks,

Jaya
Jena,

Please ask the sponsor:

- Please submit the SAS transport files (or if submitted indicate where the files are located) for the BE study BON-P6-262 data.

DSI requested for:

- DSI inspection is requested for the BE study BON-P6-262. The site details are as follows:

  **Clinical facility:**
  Algorithm Pharma Inc.
  1200 Beaumont Ave.
  Mount Royal, Quebec, Canada
  H3P 3P1

  **Analytical site:**
  b(4)

Thanks,

Jaya
REQUEST FOR CONSULTATION

TO (Division/Office):
OSE
tt. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE: 5/20/08
IND NO.:

NDA NO.:
20-866

TYPE OF DOCUMENT:
Labeling (PI, PPI, carton & container)

DATE OF DOCUMENT:
4/13/08

NAME OF DRUG:
Bromocriptine mesylate

PRIORITY CONSIDERATION:
S

CLASSIFICATION OF DRUG:
Anti-diabetic

NAME OF FIRM: VeroScience, LLC

DESIRED COMPLETION DATE:
8/15/08

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE-NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW): Labeling re-submission

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/Epidemiology Protocol
- Drug use & e.g. population exposure, associated diagnoses
- Case reports of specific reactions (List below)
- Comparative risk assessment on generic drug group
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Approvable letter for this NDA issued on 10/15/1999. Re-submission dated April 13, 2008. Please review and comment prn on all proposed LBL. Each section (PI, PPI, carton & container) is available via EDR. UFGD is October 15, 2008.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
- DFS ONLY
- HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
5/20/2008 02:08:48 PM
REQUEST FOR CONSULTATION

TO (Division/Office): OSE
tt. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE
5/20/08

IND NO. NDA NO. 20-866

TYPE OF DOCUMENT Tradename Proposal

DATE OF DOCUMENT 4/13/08

NAME OF DRUG Bromocriptine mesylate
PRIORITY CONSIDERATION S

CLASSIFICATION OF DRUG Anti-diabetic

DESIRED COMPLETION DATE 8/15/08

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY

- PRE-ND A MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT

- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW): Trade name review

II. BIOMETRICS

STASTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

STASTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Approvable letter for this NDA issued on 10/15/1999. At this time, the tradename “Cycloset,” was acceptable. Please evaluate again; the UFGD is October 15, 2008. All labeling is available via EDR under April 13, 2008, resubmission.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
- DFS ONLY
- X HAND

SIGNATURE OF RECEIVER
SIGNATURE OF DELIVERER
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/s/

Jena Weber
5/20/2008 02:04:06 PM
NDA 20-866

NDA ACKNOWLEDGMENT

VeroScience, LLC
Attention: Anthony H. Cincotta, Ph.D.
President and CSO
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cycloset (bromocriptine mesylate) 0.8 mg Tablets

Date of Application: April 13, 2008

Date of Receipt: April 15, 2008

Our Reference Number: NDA 20-866

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 15, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism & Endocrinology Products  
5901-B Ammendale Road  
Beltville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see [http://www.fda.gov/cder/ddms/binders.htm](http://www.fda.gov/cder/ddms/binders.htm).

If you have any questions, please call me at 301-796-1306.

Sincerely,

(See appended electronic signature page)

Jena M. Weber  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
5/5/2008 01:06:52 PM
April 13, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 - Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866, Amendment 29 — Complete Response to FDA approvable letter
Cycloset™ (bromocriptine mesylate) for type 2 diabetes
[Paper and Electronic Submission]

Dear Dr. Parks,

With this submission, VeroScience LLC (VeroScience) is filing a Complete Response to the Agency's approvable letter for this NDA 20-866, dated October 15, 1999. This NDA was originally filed by the first sponsor, ErgoScience Corp. (Ergo) on August 18, 1997. The Agency issued an approvable letter to the NDA with the major requirement for approval being to conduct a large, simple safety study of Cycloset™ in subjects with type 2 diabetes. Ergo transferred the NDA to PLIVA d.d. (PLIVA) of Zagreb, Croatia in November of 2003. PLIVA then met with the Agency in May 2004 to further the FDA discussions begun with Ergo respecting the study design of the Cycloset™ safety trial. VeroScience collaborated with PLIVA on the study design and execution and the safety trial was initiated in July of 2004. PLIVA then transferred ownership of the NDA to VeroScience in May of 2006 and VeroScience completed the trial (last subject out) in January of 2007 and unblinded the dataset for the trial on May 25 of 2007.

By agreement with Division staff, the large safety trial report (Study No. 165-AD-04-03-US-1) was submitted on December 12, 2007 as Amendment 27 to the NDA and the datasets for this study were filed as amendment 28 in March of 2008. All other issues listed in the approvable letter are addressed in this submission, including a systematic update from the literature, World Health Organization and FDA MedWatch databases of safety data respecting bromocriptine (the active agent in Cycloset™) use over the last 30 years.

In addition to addressing all the requirements from the approvable letter, other changes have taken place over the development period, which necessitate the filing of additional information in this submission. These issues were addressed with the Agency at a Type B meeting held on February 21, 2007 and are as follows.

Section 4 of the pending NDA is updated to provide for Patheon as the manufacturer of commercial product after approval. Ergo utilized Geneva Pharmaceuticals Inc. of Broomfield, CO to manufacture the Cycloset™ product for the clinical studies that were submitted in the originally filed NDA 20-866. Upon transfer of Ergo ownership of the NDA to PLIVA in November, 2003, PLIVA became the new manufacturer of Cycloset™ for subsequent clinical studies, including the large safety trial (Study No. 165-AD-04-03-US-1) and manufacturing was
Results for the primary endpoint are displayed in table 14.2.1.1. With the 2:1 randomization, 176 Cycloset™ and 98 placebo subjects experienced a SAE, yielding a rate ratio of 0.88 and a hazard ratio of all cause SAE of 1.023 (96% one sided confidence limit of 1.27). For the secondary endpoint, composite cardiovascular SAEs, 31 events were confirmed by adjudication for the Cycloset™ group (1.5%) and 31 events were confirmed for the placebo group (3.0%), yielding a rate ratio of 0.5 and a hazard ratio of 0.566 with a 96% one-sided confidence limit of 0.88. As can be seen from table 14.2.2.1, incidence rate for each component of the cardiovascular composite was reduced in the Cycloset™ treated patients. Finally, following 6 months on study drug, subjects receiving Cycloset™ treatment (n= 121) experienced an HbA1c reduction of -0.674 from baseline versus an increase for placebo-treated subjects (n = 71) of 0.015 to give a placebo-adjusted change from baseline of -0.69 (P <0.0001). Of these Cycloset treated subjects, 39% (vs. 11% placebo) reached the ADA goal of HbA1c of ≤ 7.0 (P<0.0007) and 53% (vs. 21% placebo) experienced a minimum reduction in HbA1c from baseline of 0.7 (p<0.0001).

We recognize that these cardiovascular safety outcomes from a “real-world” study design are particularly important in the context of the chronic and progressive nature of T2DM. It is of note that these controlled trial results are very consistent with the cardiovascular-related findings of a case cohort controlled analysis of the UK GPRD database, which was previously submitted to the NDA.

We will move quickly to finalize the safety study report and amend the NDA. We thank you for the contributions that you and your colleagues have made to designing and analyzing this study. We look forward to your continued assistance as offered at our last Type B meeting in February of this year. If there are any questions regarding this information, please feel free to contact me at 617-966-8413 or email me at Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, Ph.D.
President and Chief Science Officer

CC:
Robert Misbin, M.D.
Jena Weber
June 1, 2007

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
    Notification of Safety Trial Completion and Results

Dear Dr. Parks,

Reference is made to our NDA 20-866: Cycloset for the Treatment of Type 2 Diabetes Mellitus.

In follow up to the very productive meeting that VeroScience held with the Agency on February 21, 2007 and as a courtesy to the Division, we wish to communicate important information to you before any other external distribution occurs. We have completed and unblinded our large safety trial of Cycloset in subjects with Type 2 diabetes. After reviewing the immediately available data, we have concluded that the results are likely to prompt substantial interest among the expert community. We are therefore enclosing tables of data for the primary and secondary safety endpoints as well as for the efficacy of Cycloset in the pre-specified metformin plus sulfonylurea-treated subpopulation. These results have not been communicated beyond our organization. We are committed to providing the finalized data set and study report to the Agency as soon as possible, and in every way, supporting the Agency’s review of this trial.

This safety trial was a 52-week, double blind, placebo-controlled, multicenter study in patients receiving a diabetes therapeutic regimen consisting of either a) diet, or b) no more than two hypoglycemic agents, or c) insulin with or without one additional oral agent that were randomized to treatment with either Cycloset™ (titrated to maximal tolerated dose of 1.6 mg to no greater than 4.8 mg daily) (n= 2,054), or placebo (n= 1,016). The primary and secondary endpoints were time to first all-cause serious adverse event (SAE) and cardiovascular SAE (defined as composite of myocardial infarction, stroke, coronary revascularization, or hospitalization for angina or congestive heart failure), respectively, which were adjudicated by an independent review committee under a defined charter, previously submitted to the Agency. This trial design set a predefined margin of non-inferiority for the primary and secondary endpoints as a hazard ratio of Cycloset™ to Placebo of 1.5. Per the Statistical Analysis Plan for the trial, an analysis of the between-treatment differences in change from baseline to week 24 in HbA1c among subjects receiving metformin and sulfonylurea and HbA1c of ≥ 7.5 but < 10.0 at baseline was also performed.
performed at their facility in Zagreb, Croatia. When PLIVA transferred ownership of the NDA to VeroScience in May of 2006 PLIVA no longer had interest in manufacturing Cycloset™. Consequently, VeroScience contracted with a new contract manufacturer, Patheon Inc. of Cincinnati, Ohio, to produce product for commercial distribution upon NDA approval. We are updating the CMC section to provide for Patheon as the manufacturer of drug product. Full details of the manufacturing and controls for the manufacture of drug product by Patheon are included in this submission.

Section 6 of the pending NDA requires updating to demonstrate bioequivalence of the to-be marketed product from Patheon to the product utilized within the clinical studies of the NDA. Again, at the Type B meeting this issue of bridging the data obtained within the NDA with the to-be marketed product from Patheon was discussed. Agreement was reached to perform a bioequivalence study to bridge the product manufactured by Patheon for marketing to the product manufactured by PLIVA and utilized in the large Cycloset™ safety trial. The bioequivalence study report (Study No. BON-P6-262) is included in this submission and we trust that the Agency will agree that the two formulations are bioequivalent.

In addition to this bioequivalence study, a bridge was needed to the original NDA data that was generated using product manufactured by Geneva Pharmaceuticals Inc. (Geneva) of Broomfield, CO in 1997. This Geneva product is no longer available and as such, at the Type B meeting agreement was reached to provide a clinical efficacy bridge using efficacy data from pre-specified efficacy subgroups within the Statistical Analysis Plan for the large safety trial (165-AD-04-03-US-1) to efficacy data from Phase 3 studies within the original NDA. The clinical bridge data are included in this submission in Section 6 and we believe you will find that the data support the consistency of efficacy response to Cycloset™ regardless of manufacturer.

As noted in the Type B meeting package and as discussed at the meeting, this complete response to the approvable letter is formatted in the same manner as the original NDA. All relevant sections are updated as necessary based on new ownership, new manufacturing and new data. This Amendment updates Sections 2, 3, 4, 5, 6, 8, 9, and 10. An Index is provided in Section 1. As agreed with the Agency, case report forms from all studies in the amendment, pharmacovigilance datasets, cited literature, and additional copies of the package insert are included on DVDs in an effort to markedly limit the number of paper volumes to this submission. These electronic data are all contained within Volume 2 of the Blue Archival Binder. These DVDs have been scanned and found to be virus-free using Symantec AntiVirus Program: 10.1.0.394 Scan Engine: 71.4.0.15 Virus Definition File: 04/13/08 rev. 3 software. Each technical review section contains a copy of Volume 1 of this submission including the Index, Draft Labeling and the Amendment Summary. The Amendment Summary contains a revised annotated package insert.

We have worked in earnest to follow the guidance and advice from the Division of Metabolic and Endocrinology Products, in the completion of this submission. VeroScience wishes to thank the Division for its attention, cooperation and guidance in this process. Should you have any questions or require any additional information regarding this submission, please feel free to contact the undersigned at (phone) 617 966 8413, (fax) 401 608 3079, or (email) Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer
### Applicant Information

**Name of Applicant:** VeroScience, LLC  
**Date of Submission:** 04/13/2008  
**Telephone No. (Include Area Code):** 401-816-0525  
**Facsimile (Fax) Number (Include Area Code):** 401-816-0524  
**Authorized U.S. Agent Name & Address:**  
**Address:** 1334 Main Road, Tiverton, RI 02878

### Product Description

**New Drug or Antibiotic Application Number, or Biologics License Application Number (if previously issued):** 20-866  
**Established Name:** (e.g., Proper name, USP/Susan name)  
**Proprietary Name** (trade name if any):  
**Chemical/Biological/Blood Product Name (if any):**  
**Cycloset**  
**(5'o)-2-Bromo-12'-hydroxy-2'-1-methylethyl)-5'-2-methylpropyl)ergotaman-3',6',18-trione**  
**Dosage Form:** Tablet  
**Strength:** 0.8 mg  
**Route of Administration:** Oral  
**Proposed Indication (s) for use:** Treatment of Type 2 Diabetes Mellitus

### Application Description

**Application Type:**  
- [ ] New Drug Application (CDA, 21 CFR 314.50)  
- [ ] Abbreviated New Drug Application (ANDA, 21 CFR 314.54)  
- [X] Biologics License Application (BLA, 21 CFR Part 601)  
**If an NDA, identify the appropriate type:**  
- [X] 505 (b)(1)  
- [ ] 505 (b)(2)  
**If an ANDA, or 505(b)(2), identify the reference listed drug product that is the basis for the submission:**  
**Name of drug**:  
**Holder of Approved Application**:  
**Type of Submission (check one):**  
- [ ] Original Application  
- [X] Amendment to a pending application  
- [ ] Resubmission  
- [ ] Pre-Submission  
- [ ] Annual Report  
- [ ] Establishment Description Supplement  
- [ ] Efficacy Supplement  
- [ ] Labeling Supplement  
- [ ] Chemistry, Manufacturing, and Controls Supplement  
- [ ] Other  
**If a Submission of Partial Application, provide letter date of agreement to partial submission:**  
**If a supplement, identify the appropriate category:**  
- [ ] CBE  
- [ ] CS-30  
- [X] Prior Approval (PA)  
**Reason for Submission:**  
**Complete Response to Approvable Letter for NDA 20-866**

**Proposed Marketing Status (check one):**  
- [ ] Prescription Product (Rx)  
- [X] Over the Counter Product (OTC)**

**Number of Volumes Submitted:** 37  
**This Application is:**  
- [ ] Paper  
- [ ] Paper and Electronic  
- [X] Electronic

### Establishment Information

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CRN), DMF number, and manufacturing steps and, if type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

(References: list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

**IND 34,661**

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**Form FDA 356h (4/06)**

**Page 1 of 4**
**This application contains the following items: (Check all that apply)**

- [x] 1. Index
- [x] 2. Labeling (check one)  
  - [ ] Draft Labeling  
  - [ ] Final Printed Labeling
- [x] 3. Summary (21 CFR 314.50 (c))
- [x] 4. Chemistry section
  - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 801.2)
  - B. Samples (21 CFR 314.50(e)(1); 21 CFR 801.2 (a)) (Submit only upon FDA’s request)
  - C. Methods validation package (e.g., 21 CFR 314.50(e)(2); 21 CFR 801.2)
- [x] 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 801.2)
- [x] 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 801.2)
- [ ] 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- [ ] 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 801.2)
- [x] 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(v); 21 CFR 801.2)
- [x] 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 801.2)
- [ ] 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 801.2)
- [x] 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 801.2)
- [ ] 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- [ ] 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (l)(2)(A))
- [x] 15. Establishment description (21 CFR Part 800, if applicable)
- [ ] 16. Debarment certification (FD&C Act 306 (k)(1))
- [x] 17. Final copy certification (21 CFR 314.50 (l)(3))
- [ ] 18. User Fee Cover Sheet (Form FDA 3397)
- [ ] 19. Financial Information (21 CFR Part 54)
- [ ] 20. OTHER (Specify)

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 600, and/or 820.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 860, and/or 805.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 800.80, and 800.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense. U.S. Code, title 18, section 1001.

**SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT**

Anthony H. Cincotta, Ph.D., President and CSO

**ADDRESS (Street, City, State, and ZIP Code)**

1334 Main Road, Tiverton, RI 02878

**Telephone Number**

(401) 816-0525

**DATE**

04/13/2008

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
3000 White Oak Drive  
Rockville, MD 20857-0034

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
NDA 20-866

VeroScience, LLC
Attention: Anthony H. Cincotta, Ph.D.
President and Chief Science Officer
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset™ (bromocriptine mesylate) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 21, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
I certify that the Field Copy of Amendment 29 to NDA 20-866 for Cycloset™ bromocriptine mesylate is an exact duplicate of Section 4 - Chemistry, Manufacturing and Controls as filed in the NDA Amendment.

Anthony H. Ciarotta, Ph. D.
President

April 13, 2008
Date
INDUSTRY MEETING MINUTES

MEETING TYPE: B
MEETING CATEGORY: Response to Approvable letter
INTERNAL MEETING DATE: Friday February 2, 2007
INDUSTRY MEETING DATE: Wednesday February 21, 2007
APPLICATION NUMBER: NDA 20-866
PRODUCT NAME: Cycloset (bromocriptine mesylate)
SPONSOR: VeroScience
MEETING CHAIR: Mary Parks, M.D., Director, Division of Metabolism & Endocrinology Products (DMEP)
MEETING RECORDER: Jena Weber, Project Manager

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D. Division Director
Robert Misbin, M.D. Clinical Reviewer
Jena Weber, BS Project Manager

Office of Biometrics II, HFD-715

Todd Sahlroot, Ph.D. Team Leader - Biometrics
Lee-Ping Fian, Ph.D. Biometrics Reviewer

Office of Clinical Pharmacology (OCP)

Qiu Wei, Ph.D. OCP Reviewer
Jim Wei, M.D., Ph.D. OCP Reviewer

VeroScience

Anthony Cincotta, Ph.D. President, Chief Science Officer
Richard Scranton, M.D., MPH Chief Medical Officer

Michael Gaziano, M.D., MPH Brigham & Women's Hospital, Principal Investigator
David Adams, Esq. Venable LLP

Regulatory Background
VeroScience has completed the acquisition of Cycloset (bromocriptine mesylate) from the former sponsor, PLIVA, d.d. (PLIVA). Notifications of the transfer of ownership for NDA 20-866 were submitted to the Agency in accordance with 21 CFR 3 14.72, and notifications were acknowledged by the Agency on June 22, 2006.
An approvable letter for NDA 20-866 was issued to Ergo Science Corp. (Ergo) by FDA on October 15, 1999. The approvable letter included a series of comments arising from the Agency's review. The Agency held a meeting with Ergo on April 6, 2000, to discuss appropriate strategies to obtain NDA approval.

**Trial Commitment**
The Agency's principal recommendation for approval was that the sponsor (Ergo) should perform a large, "simple" clinical trial (SCT) to show that bromocriptine treatment does not increase the risk of serious cardiovascular events in patients with T2DM. VeroScience is now completing the agreed SCT to address the aforementioned safety concern. A planned interim analysis of the primary and secondary endpoints of the trial, including cardiovascular safety, was conducted in July 2006, and the trial's last patient will finish therapy on December 27, 2006.

**Meeting Purpose:**
a) review the Cycloset amended NDA 20,866 filing plans of the new sponsor, VeroScience and
b) confirm that the Agency requirements for filing a complete and final response to the approvable letter and requests of the May 11, 2004, meeting will have been met by following the Sponsor's plans for filing, c) brief discussion regarding the manufacture of Cycloset by a U.S. manufacturer, Pathon Inc. VeroScience seeks the Agency's concurrence with VeroScience's plan to utilize this manufacturer for submission of the registration batches with the final response amendment to the NDA and to use this supplier for commercialization of the Cycloset product. VeroScience has just submitted protocols and an overall proposal for linking the versions of the drug product used in the clinical trials with the product to be marketed.

**Objectives and Expected Outcomes**
1. Provide status of current ongoing clinical safety trial (last subject out of study on December 27, 2006), and discuss timeline for submission of approvable letter response.
2. Receive any further comments regarding the proposed plan for bioequivalence (bridging) studies of clinical studies supply and commercial product.
3. Achieve FDA acceptance of the finalized Statistical Analysis Plan for the ongoing clinical safety trial to now include secondary efficacy outcomes.
4. Receive FDA acceptance of sponsor's plans for new manufacturing site for registration batches of cycloset and commercial product focusing on stability data available at the time of filing.
5. Receive FDA acceptance of plan for filing a final response to the AE letter.

**Proposed Indications:**
The proposed indications for Cycloset (bromocriptine mesylate) are:
(a) As monotherapy to lower blood glucose in patients with type 2 diabetes mellitus whose hyperglycemia is inadequately controlled with diet and exercise;
(b) For use in combination therapy with a sulfonylurea and/or metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus therapy with any of the following agents: metformin, sulfonylurea, or bromocriptine.

**Note:** VeroScience was in agreement with the Agency's internal response to questions 1, 3, 4, and 6. Meeting discussion was mostly central to questions 2 and 5.

**Questions**
1. In addressing the sole deficiency of the NDA approvable letter of October 15, 1999, the
sponsors of NDA 20-866, conferred with FDA to design a large, "simple" safety trial of Cycloset
(bromocriptine mesylate). Agreement was reached on the design of the trial at the
May 11, 2004, meeting between representatives of PLIVA and FDA. The protocol was finalized
and submitted to the FDA on June 25, 2004, (TND Serial No.0200). VeroScience has finalized
the Statistical Analysis Plan (SAP) for the safety trial, which is submitted within the briefing
document for this meeting request, for FDA review and concurrence. VeroScience has
concluded that this analysis plan will support a robust determination of the safety study
objectives that will allow the remaining deficiency to be resolved. Does FDA agree?
FDA Response: As requested in the meeting minutes on April 6, 2000, 'Near complete
follow-up will be critical with ascertainment of vital and critical status, including as
myocardial infarction (MI's), stroke and death.' The submission should include
documentation of all events including events following a time-to-event endpoint and events
occurring following discontinuation of study drug.

Analyses of primary and secondary endpoints are time to event analyses of the hazard ratio
between Cycloset and placebo. As a sensitivity analysis, incidence rates should be compared
between Cycloset and placebo using risk ratios.
From 2/21/07 meeting: VeroScience acknowledged that a sensitivity analysis will be
provided.

2. In the approvable letter of October 15, 1999, of NDA 20-866, the Agency requested that the
sponsor update the NDA with current safety information on the new drug. VeroScience plans to
do so, in part, by providing such information from World Health Organization, U.S. Food and
Drug Administration, published literature and pharmaceutical pharmacovigilance databases on
this topic. Also, VeroScience will provide available data from analyses of a large prospective,
cohort-controlled epidemiological study from the United Kingdom General Practitioners
Research Database of myocardial infarction rates in subjects exposed to bromocriptine.
Moreover, VeroScience plans to provide comparison tables of safety data from the ongoing large
"simple" safety trial versus the safety data currently in the NDA. The comparison table shells are
provided in the briefing document. The above data sets will be compiled into an Overall
Summary of Safety (separate from and in addition to the safety trial study report) as part of the
amendment to the NDA. VeroScience has concluded that this approach satisfies the Agency's
request for updating the safety information on Cycloset Does the FDA agree?
FDA Response: The proposal is adequate with respect to the issues raised in the
approvable letter. But a new concern, valvulopathy, has emerged and should be addressed.
Whether ECHO studies were done or not should be stated; a sub-study including coding on
valvulopathy may be required. Patients still taking drug could constitute a population in
which to address this issue.
From 2/21/07 meeting, add:
- Bromocriptine – antagonist of the 5-HT2B receptor.
- Previous echo study submitted to IND 34,660 (YY 1999);
  Cycloset 49 subjects, 49 controls for 6 month study showed no valvular abnormalities.
- Kim et al (Movement Disorders, 21, 2006) Echo study;
  22 Bromocriptine, 36 Pergolide (lower dose), 20 age matched control;
  Conclusion – no significant valvular abnormalities.
- Post-marketing surveillance – estimated _______ person year exposures (France);
  1 reported case of severe TR (mild MR & AR) with bromocriptine (40 mg – 5 years).
WHO adverse reporting - no cases of valvular heart disease solely attributed to bromocriptine
(1 case of mitral stenosis while taking bromocriptine and pergolide).

The Division stated that these additional data are likely sufficient to address any concerns of valvuleopathy associated with bromocriptine use and recommended that they be incorporated in the resubmission to the NDA.

3. Metformin has generally become the preferred first line treatment of T2DM. All other approved oral therapies for T2DM have indications for combination with metformin. Because metformin was not yet approved during the development of bromocriptine mesylate, no clinical trials were performed with metformin. FDA had indicated at the May 11, 2004, meeting with PLIVA that glycemic control - efficacy data of Cycloset in subjects on metformin would be helpful in labeling of the drug. The availability of a large cohort of subjects on the combination of metformin plus sulfonylurea and Cycloset in the safety trial could provide data to support information on efficacy as well as safety of this combination.

VeroScience has specified in the final SAP provisions for the analysis of efficacy data from the cohort on metformin plus sulfonylurea and cycloset. This plan is submitted within the briefing document for this meeting request for FDA review and concurrence. VeroScience has concluded that these data, so analyzed, would provide information of cycloset efficacy as well as safety in a population of subjects treated with metformin. Does FDA agree?

FDA Response: This will be a review issue; language to the appropriate section(s) of the PI will reflect the analysis of submitted data.

From 2/21/07 meeting: the SAP appears acceptable on face-value. However, the submission must contain clean efficacy data. In addition to previously compiled/ submitted data, a robust study to support bridging, could prove to be clinically beneficial as a link supporting efficacy (a new trial using metformin could be considered). Also see response to question 5.

4. In its October 15, 1999 approvable letter, FDA provided a short list of questions related to manufacturing of the and a scored 0.8 mg tablet dosage form. VeroScience will not be pursuing or seeking approval for manufacturing and commercialization of either the 0.8 mg tablet dosage forms in its current amended NDA filing. VeroScience has concluded that no further responses are necessary to address these particular manufacturing queries from the Agency. Does the FDA Agree?

FDA Response: Yes.

5. The previous sponsor (Pliva d.d.) was also the manufacturer of the Cycloset product utilized in the ongoing safety trial. However, Pliva d.d. is no longer manufacturing Cycloset. Consequently, VeroScience has contracted with a new U.S. manufacturer for the manufacture of registration batches and commercialization of Cycloset product. As a result of moving the manufacture of Cycloset to a new facility, the amended NDA will compare three different versions of drug product:

- The product used for the original clinical trials in the originally filed NDA
- The product used in the current safety study, and
- The product proposed for marketing.
VeroScience has provided a plan for bridging of bioequivalence among these three versions. These protocols and the overall bridging approach were submitted recently for review under the Cycloset IND (Serial No. 0321). Does the FDA agree with these plans?

**FDA Response:** We have never granted a pivotal BE assessment based on cross-study comparison. Therefore, the proposed bioequivalence study to demonstrate BE between the products used in original NDA submission and the products used in the ongoing safety trial is not acceptable. Pivotal bioequivalence needs to be established in a single study. If the products used in the pivotal clinical trials in the original NDA are no longer available, a clinical efficacy bridge study is recommended.

**From 2/21/07 meeting:** the company stated that a non-traditional approach was taken to assess BE of this product due to the 3 different sponsors and 3 different manufacturing sites. The current manufacturing contractor is Patheon Inc. (Cincinnati, OH), and provides for the same ingredients, formulations, chemical features, etc. The company provided a dissolution profile of tablets from three manufacturing sites. A BE trial of the PLIVA product versus the Patheon product will be conducted.

FDA emphasized that the dissolution profile for Geneva site was from historic data. Such dissolution analysis for f2 calculation across studies is not valid. The site change is considered a Level 3, which requires an in-vivo BE study. The originally proposed BE study only can be used as supportive.

This method of bridging between formulations is not acceptable. While the Division recognizes that there is no other alternative since the initial drug product is no longer available, the company must provide sufficient evidence supporting efficacy of the to-be-marketed formulation. There was extensive discussion surrounding efficacy analyses from the cardiac safety study. The medical and statistical reviewers expressed concern that confounding effects of background therapy or study design will not permit a reliable estimate of efficacy. We cannot commit that this proposal is adequate for establishing efficacy and it will therefore be a review issue. Alternatively, the company can conduct an efficacy study evaluating the effect of Cycloset in combination with metformin. As there is a high likelihood that these two drugs would be used together in practice, a well-designed study to evaluate efficacy (and safety) may overcome the problems of bridging efficacy through indirect bioequivalence studies and analysis of your safety study.

6. VeroScience is moving the manufacture of Cycloset to a new facility, Patheon Inc., in Cincinnati, Ohio. VeroScience will provide information and the plan for the transfer of manufacturing to this facility as well as for the stability testing of NDA and commercial drug products in an upcoming IND submission on CMC in January. VeroScience will also be providing information on the stability data available at the time of the anticipated NDA amendment submission. Does the FDA agree with these plans?

**FDA Response:** Yes, we agree with this proposal.
7. VeroScience intends to file a final response to the Agency approvable letter for NDA 20-866 in the second quarter of 2007. It will consist of the results of the large "simple" safety trial (both safety and efficacy as detailed in the study SAP), summaries of NDA safety and efficacy data (including study reports from those trials not completed at the time of the original NDA filing), a world-wide database compilation on clinical safety of bromocriptine, the complete responses to all approvable letter queries, as well as the information and data to support the new manufacturing facility and the commercial drug product, and revised labeling for the drug product. VeroScience has concluded that these data and information will address all deficiencies and questions raised by the Agency so that the review of NDA 20-866 may be completed. Does the FDA agree?

FDA Response: This will be a review issue.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
3/1/2007 02:27:43 PM
NDA 20-866

VeroScience LLC  
Attention: Anthony H. Cincotta, Ph.D.  
1334 Main Road  
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Cycloset (bromocriptine mesylate).

We also refer to your December 21, 2006, correspondence, received December 22, 2006, requesting a meeting to discuss your final response to our approvable letter dated October 15, 1999.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled Formal Meetings with Sponsors and Applicants for PDUFA Products (February 2000). The meeting is scheduled for:

Date: Tuesday February 13, 2007  
Time: 3:30 – 5:00 pm  
Location: White Oak Campus, Building 22  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

Tentative CDER participants:

Blair Fraser, Ph.D.  
Branch Chief, Chemistry  
Robert Meyer, M.D.  
Office Director (ODE-II)  
Robert Misbin, M.D.  
Clinical Reviewer  
Stephen Moore, Ph.D.  
Chemistry  
Mary Parks, M.D.  
Division Director (DMEP)  
Lee-Ping Pian, Ph.D.  
Biometrics  
Curt Rosebraugh, M.D.  
Deputy Office Director (ODE-II)  
Todd Sahlroth, Ph.D.  
Team Leader – Biometrics  
Wei Qiu, Ph.D.  
Biopharmaceutics Reviewer  
Jena Weber, BS  
Project Manager  
Jim Wei, M.D., Ph.D.  
Acting Team Leader, Biopharmaceutics
Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Jena.Weber@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards my number (301-796-1306) to request an escort to the conference room.

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
1/5/2007 04:20:12 PM
NDA 20-866

VeroScience LLC
Attention: Anthony Cincotta, Ph.D.
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

We acknowledge receipt on May 18, 2006, of your May 16, 2006, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: Cycloset™ (bromocriptine mesylate) Tablets

NDA Number: 20-866

Name of New Applicant: VeroScience LLC

Name of Previous Applicant: Pliva Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate VeroScience LLC as the sponsor of record for this application.

All changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. Refer to the Guidance for Industry: Changes to an Approved NDA or ANDA for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of all submissions to this application.
Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

cc: Pliva Inc.  
72 Eagle Rock Avenue; P.O. Box 371  
East Hanover, NJ 07936
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Jena Weber
6/22/2006 08:35:11 AM
NDA 20-866

Attention: 

Dear Mr. 

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 11, 2004. The purpose of this meeting was to discuss the Agency’s recommendation that a large, simple clinical trial be conducted in order to address concerns of a possible increase in myocardial infarction (MI) occurring in patients receiving bromocriptine.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-827-6411.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
MEMORANDUM OF MEETING MINUTES

MEETING DATE: Tuesday May 11, 2004
TIME: 9:30 pm
LOCATION: 17-05
APPLICATION: NDA 20-866
TYPE OF MEETING: Type A
MEETING CHAIR: David Orloff, M.D., Division Director, Metabolic and Endocrine Drug Products (DMEDP), HFD-510
MEETING RECORDER: Jena Weber, Project Manager

Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510:

David Orloff, M.D. Division Director
Robert Misbin, M.D. Clinical Reviewer
Bruce Stadel, M.D. Clinical Reviewer
Jena Weber, BS Project Manager
Kati Johnson, R.Ph. Chief, Project Management Staff

Office of Biometrics II, HFD-715

Todd Sahlroot, Ph.D. Team Leader – Biometrics
Lee-Ping Pian, Ph.D. Biometrics Reviewer

PLIVA:

Lidija Brnic, M.D. Regulatory Affairs
Donald Waters, Ph.D. Clinical Research
Janet Peterson, Ph.D. Clinical Research
Marko Kolega, M.D. Project Director
Anthony Cincotta, Ph.D. Consultant
Marcia Testa, M.D., Ph.D. Consultant – Harvard Medical School
Donald Simonson, M.D. Principal Investigator

Proposed Indication: As an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus.

Purpose of the Meeting: To obtain feedback on the design of the proposed clinical study to evaluate the potential for significant increase in the risk of serious cardiac adverse events in patients receiving bromocriptine; analyses and/or additional data needed to establish CV safety of bromocriptine; miscellaneous Agency advice in pursuing NDA approval for this product.
Background: NDA 20-866 was initially submitted on August 18, 1997. A not approvable letter citing deficiencies of efficacy and safety (particularly possible adverse cardiac effects) was issued on November 20, 1998. The company provided a complete response to this letter on April 15, 1999. An approvable letter was issued by the Agency on October 15, 1999. Deficiencies in the clinical, biopharmaceutics, and pharmacology and toxicology sections of the application were cited.

1. Based on the Agency’s feedback as summarized in the approvable letter to NDA 20-866 dated October 15, 1999, and as expressed in discussions that occurred during the meeting held on April 6, 2000, it is “PLIVA’s understanding” that FDA has agreed that the application for Cycloset® may be approved pending (1) successful completion of and submission of data from a clinical trial to evaluate the potential for a significant increased risk of serious adverse events (including MI, stroke, and death) with Cycloset® treatment and (2) submission of updated safety data and draft labeling along with adequate data to address the biopharmaceutic, pharmacology, and toxicology deficiencies noted in the 1999 approvable letter. Is this assessment of FDA’s position accurate?

FDA Response: In general, yes. However, we have specific comments at this time:

1. The population enrolled in this trial must be representative of the broad population of subjects who will use this drug; for example, by severity and duration of diabetes and by use of other anti-diabetic medications.

2. A Phase 4 program studying the addition of Cycloset to metformin should be considered. Concomitant usage of insulin and Cycloset is not appropriate.

3. Provide interpretations for the possible outcomes of the proposed non-inferiority trial – in particular, for the outcome where there is evidence of adverse effects, but less than significant according to the prespecified statistical test.

4. Justify the proposed duration of the trial according to the relationship between time since starting bromocriptine and the occurrence of myocardial infarction, stroke, and other cardiovascular events, using randomized trial and observational study data.

5. Justify the proposed inclusion/exclusion criteria in relation to the proposed treatment population, as defined by the proposed labeling.

6. Justify using discontinuation rates rather than event rates for outcomes, or change to event rates, or change to event rates. Vital and clinical status should be ascertained at the closure of the trial.

7. Show the power of the proposed trial for myocardial infarction, and stroke, in addition to the currently proposed outcome.

8. Provide an estimate for the length of time needed to complete the entire study.

9. Provide a stopping rule.
2. PLIVA believes that the design and size of the proposed clinical trial as outlined in the protocol submitted on March 4, 2004, are appropriate to meet the stated objectives, and that these objectives are appropriate to address the concerns that the Agency has expressed regarding the potential risk of serious adverse events (including MI, stroke, and death) that may be associated with Cycloset® treatment. Does FDA agree? 
FDA Response: FDA recommends a 1-year trial with at least 2000 patients treated with Cycloset.

3. PLIVA believes that if the proposed clinical trial has a positive outcome (i.e., the study demonstrates with 90% power that the event rate for Cycloset® is at least as low as the event rate for placebo), the results from this proposed trial, along with the previously submitted data on clinical efficacy and safety, as well as updated labeling and data on safety, biopharmaceutics, pharmacology, and toxicology, should result in approval of NDA 20-866. Does FDA agree? 
FDA Response: The non-inferiority margin (1.5) represents an increase of 22 events or equivalently a 50% increase in relative risk. This allowable risk increase may be too liberal. The margin could be tightened by increasing the length of the trial from 6 months to one year. For example, assuming a doubling of incidence rates from 3% to 6% under linearity, 22 events represent a 25% increase in relative risk.

Following additional internal discussion of the appropriate Type I error rate, the analysis should be conducted at a two-sided alpha = 10%.

A futility analysis should be added to the interim analysis plan.

ost meeting comment: The Division concurs with the Sponsor’s minutes of the May 11, 2004, meeting submitted to the Agency on May 27, 2004.
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/s/

Jena Weber
6/10/04 09:39:45 AM
NDA 20-866

Attention:

Dear

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate) Tablets.

We also refer to your March 4, 2004, correspondence, received March 5, 2004, requesting a meeting to discuss our recommendation that you conduct a “large, simple clinical trial to address the concern of possible increased myocardial infarction (MI) in patients receiving bromocriptine.”

Please note that the date, time and room location for this meeting has been changed to:

Date: Tuesday May 11, 2004
Time: 9:30 AM
Location: Parklawn Building, Room 17-05

Two additional CDER participants have also been added:

Judy Staffa, Ph.D. Office of Drug Safety (Epidemiology)
Sandra Birdsong Office of Drug Safety, Project Manager

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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/s/

Jena Weber
4/9/04 02:02:34 PM
REQUEST FOR CONSULTATION

TO (Division/Office): ODS (Room 15B-08, PKLN Bldg.)
Mail: Sandra Birdsong, HFD-430/Attn: Judy Staffa, Ph.D., HFD-410

FROM: Jena Weber, HFD-510
(301) 827-6422

DATE March 26, 2004
IND NO. NDA NO. TYPE OF DOCUMENT DATE OF DOCUMENT
March 4, 2004
NAME OF DRUG Cyclosett (Bromocriptine Mesylate)
PRIORITY CONSIDERATION High
CLASSIFICATION OF DRUG Type 2 diabetes
DESIRED COMPLETION DATE April 9, 2004

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE-nda MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH
- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH
- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Please evaluate a new Clinical Study Protocol, CYCSS-04, A Randomized, Double-Blind, Placebo-Controlled Trial to Assess Safety and Tolerability during Treatment of Type 2 Diabetes with Usual Diabetes Therapy and either Cyclosett or Placebo. Information requested by MO for a meeting with the sponsor. Feel free to speak with Dr. Bruce Stadel, medical officer, regarding this consult @301-827-6417.

SIGNATURE OF REQUESTER
Dr. Mary Parks, Deputy Director, HFD-510

SIGNATURE OF RECEIVER
M.A. Simoneau, Reg. PM for Jena Weber
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/s/

Mary Parks
3/26/04 09:59:11 AM
NDA 20-866

Attention:

b(4)

Dear b(4)

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclosel (bromocriptine mesylate) Tablets.

We also refer to your March 4, 2004, correspondence, received March 5, 2004, requesting a meeting to discuss our recommendation that you conduct a “large, simple clinical trial to address the concern of possible increased myocardial infarction (MI) in patients receiving bromocriptine.”

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type “A” meeting as described in our guidance for industry titled Formal Meetings with Sponsors and Applicants for PDUFA Products (February 2000). The meeting is scheduled for:

Date: Monday April 12, 2004
Time: 10 AM
Location: Parklawn Building, 3rd floor conference room “B”

Tentative CDER participants:

- David Orloff, M.D. Division Director, HFD-510
- Robert Misbin, M.D. Clinical Reviewer
- Bruce Stadel, M.D. Clinical/Epidemiology Reviewer
- Todd Sahlroot, Ph.D. Team Leader – Biometrics
- Lee-Ping Pian, Ph.D. Biometrics Reviewer
- Jena Weber, BS Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Weberj@eder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Ms. Jena Weber, 301-827-6422.
Provide the background information for this meeting (three copies to the NDA and 8 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by March 19, 2004, we may cancel or reschedule the meeting.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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/s/

--------------------------
Jena Weber
3/11/04 01:16:21 PM
MEMORANDUM

DATE: January 5, 2004

TO: Memo to the File

FROM: Lina AlJuburi, Regulatory Health Project Manager; HFD-510

SUBJECT: Change IND status from terminated to active due to change in sponsorship for IND 34,661 for Bromocriptine Mesylate Tablets and change in sponsorship for IND 34,661 and NDA 20-866

A report request was sent to the sponsor of this IND, Ergo Science Corporation, on February 6, 2003, to fulfill the requirement for an annual report of progress of the investigation. This letter was returned for an undeliverable address and no other address was on file for this application. Therefore, the application was considered terminated.

On December 15, 2003, a request was received from the new sponsor, PLIVA Inc., with the required information from Ergo Science Corporation to transfer sponsorship of pending NDA 20-866 and IND 34,611 for Bromocriptine Mesylate Tablets.

Because of this updated information, the status of IND 34,661 needs to be changed from terminated to active. PLIVA Pharmaceuticals has been notified in writing of the requirements to submit annual reports and was asked to submit one within 30 days of receiving the letter acknowledging the transfer of sponsorship.

The sponsor information needs to be updated for both IND 34,661 and NDA 20-866 to include:

New Sponsor Information

PLIVA Inc.
72 Eagle Rock Avenue
P.O. Box 371
East Hanover, NJ 07936

Contact Person: Roger Schwede, VP of R&D and Regulatory Affairs
Phone #: 973-599-4352
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/s/

Lina Aljuburi
1/5/04 02:19:06 PM
CSO
NDA 20-866

Ergo Research Corporation
Attention:  David Burt
President and CEO
Jefferson Office Park; 780 Turnpike Street, Suite 205
North Andover, MA 08145

Dear Mr. Burt:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocryptine) capsules.

Our letter of October 15, 1999, notified you that your application was approvable. We have not received a complete response to this letter. We also refer to the minutes from our meeting of April 6, 2000, in which we stated that any future protocols for studies that you wish to conduct should be submitted to the Agency for our review and comment before these trials commence. We note that you have not submitted any proposed protocols.

If you do not submit a complete response, or withdraw the NDA under 21 CFR 314.65, within 30 days, we will withdraw this application under 21 CFR 314.65. Withdrawal does not prejudice refiling of the application. You may reference the information contained in the withdrawn application in any future submission.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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/s/

Jena Weber
3/18/03 12:50:20 PM
NDA 20-866

Ergo Research Corporation
Attention: David Burt, President and CEO
Jefferson Office Park
780 Turnpike Street, Suite 205
North Andover, MA 08145

Dear Mr. Burt:

We received your July 12, 2002, correspondence on July 12, 2002, requesting a meeting to discuss the contents of the approvable letter issued by the Agency on October 15, 1999, and your development plans for this product in order to obtain approval of this NDA. We considered your request and concluded that the meeting is unnecessary. Please reference the minutes from our meeting of April 6, 2000, in which we stated that any future protocols for studies that you wish to conduct should be submitted to the Agency for our review and comment before these trials commence.

If you disagree with our decision, you may discuss the matter with Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled Formal Dispute Resolution: Appeals Above the Division Level (February 2000). The guidance can be found at http://www.fda.gov/der/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation ODE II
Center for Drug Evaluation and Research
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/s/

Mary Parks
8/6/02 04:14:06 PM
for Dr. Orloff
MEMORANDUM OF MEETING MINUTES

MEETING DATE: Thursday April 6, 2000
TIME: 2:00 pm
LOCATION: 3rd floor Parklawn, Conference Room “M”
APPLICATION: NDA 20-866 – Cycloset (bromocryptine)
MEETING CHAIR: David Orloff, M.D., Deputy Director, Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510
MEETING RECORDER: Jena Weber, Project Manager

FDA ATTENDEES, TITLES, Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510 and others:

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solomon Sobel, M.D.</td>
<td>Deputy Director</td>
<td>ORU, HFD-020</td>
</tr>
<tr>
<td>John Jenkins, M.D.</td>
<td>Office Director, ODE II</td>
<td>HFD-102</td>
</tr>
<tr>
<td>Stephen Fredd, M.D.</td>
<td>Deputy Division Director</td>
<td>HFD-110</td>
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<tr>
<td>Judy Staffa, Ph.D.</td>
<td>OPDRA</td>
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<tr>
<td>Evelyn Rodriguez, M.D.</td>
<td>OPDRA</td>
<td>HFD-440</td>
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<tr>
<td>Robert Misbin, M.D.</td>
<td>Clinical Reviewer</td>
<td>DMEDP, HFD-510</td>
</tr>
<tr>
<td>Bruce Schneider, M.D.</td>
<td>Clinical Reviewer</td>
<td>DMEDP, HFD-510</td>
</tr>
<tr>
<td>Saul Malozowski, M.D.</td>
<td>Team Leader, Clinical</td>
<td>DMEDP, HFD-510</td>
</tr>
<tr>
<td>William Koch, R.Ph.</td>
<td>Project Manager</td>
<td>DMEDP, HFD-510</td>
</tr>
<tr>
<td>Jena Weber, BS</td>
<td>Project Manager</td>
<td>DMEDP, HFD-510</td>
</tr>
<tr>
<td>Lee-Ping Pian, Ph.D.</td>
<td>Biometrics Reviewer</td>
<td>HFD-715</td>
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<tr>
<td>Todd Sahroot, Ph.D.</td>
<td>Biometrics Team Leader</td>
<td>HFD-715</td>
</tr>
<tr>
<td>Kathleen Uhl, M.D.</td>
<td>OND</td>
<td>HFD-970</td>
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ErgoScience Corporation ATTENDEES AND TITLES:

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<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
<tr>
<td>David Burt</td>
<td>President, ErgoScience</td>
</tr>
<tr>
<td>Marcia Testa, M.D., Ph.D.</td>
<td>Harvard School of Public Policy</td>
</tr>
<tr>
<td>Anthony Cincotta, Ph.D.</td>
<td>Director, ErgoScience</td>
</tr>
<tr>
<td>David Adams</td>
<td>Counsel to ErgoScience</td>
</tr>
</tbody>
</table>

Proposed Indication: For the treatment of patients with Type 2 Diabetes Mellitus.
**Purpose of meeting:** Strategies for proceeding with the development of Cycloset for NDA approval.

**Background:** NDA 20-866 was initially submitted on August 18, 1997. A not approvable letter citing deficiencies of efficacy and safety (particularly possible adverse cardiac effects) was issued on November 20, 1998. The company provided a complete response to this letter on April 15, 1999. An approvable letter was issued by the Agency on October 15, 1999. Deficiencies in the clinical, biopharmaceutics, and pharmacology and toxicology sections of the application were cited.

**General Discussion Points:**

As specified in our approvable letter, a large, simple trial design to address clinical deficiencies was suggested. A safety study enrolling approximately 3000 subjects (diagnosed with type 2 DM) may suffice. Sample size should be justified based on study efficacy and safety objectives. The Agency will require a minimum of 2000 subjects on drug, and 1000 on placebo, treated for 6 months to 1 year. Near complete follow-up will be critical with ascertainment of vital and critical status, including as myocardial infarction (MI’s), stroke and death.

An independent safety data monitoring board should be established. In addition, ADA guidelines regarding goals of therapy and standards of patient care should be followed. Patients may be enrolled who are currently taking anti-diabetic medications, but NOT thiazolidinediones (TZD’s).

The protocol(s) for this/these studies should be submitted to the Agency for our review and comment before the trial(s) commence(s).

If the sponsor pursues a lipid-lowering indication, results of and adequate and well-controlled studies must be presented.

**Conclusions:** The sponsor will submit a detailed, study protocol(s) for Agency review and comment.
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/s/

David Orloff
8/1/02 02:56:58 PM
Endocrinologic and Metabolic Drugs Advisory Committee #70

Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, MD

May 14, 1998

Agenda

NDA 20-966, Ergoset™ (bromocryptine) Ergo Science

8:00 Call to Order, Introductions, Opening Comments
Robert Sherwin, M.D., Acting Chair
Endocrinologic and Metabolic Drugs Advisory Committee
Meeting Statement: Kathleen Reedy, Executive Secretary
Endocrinologic and Metabolic Drugs Advisory Committee

8:15 Open Public Hearing

8:45 Ergo Science Presentation

10:15 Break

10:30 FDA Presentation
Medical Review: G. Alexander Fleming, M.D., Group Leader,
Division of Metabolic and Endocrine Drug Products

Statistical Review: Lee Ping Pian, Ph.D.,
Office of Epidemiology and Biostatistics
Division of Biometrics II

11:30 Lunch

1:00 Discussion and Questions

Break

5:00 Adjourn
1. Are the study designs adequate to assess the efficacy and safety of this drug for the proposed patient population?

2. What is the clinical significance of the reduced HbA1c levels observed in the pivotal studies?

3. What is the appropriate role of the prospectively stated responder analysis in the evaluation and/or labeling of this therapy?

4. Based on the efficacy and safety data presented, and your assessment of the overall benefits compared to the risks of bromocryptine therapy, do you recommend that this drug be approved for use in the proposed patient population?

5. If approval is recommended, what measures should be taken after approval to refine understanding of this therapy's efficacy and resolve its remaining safety issues.